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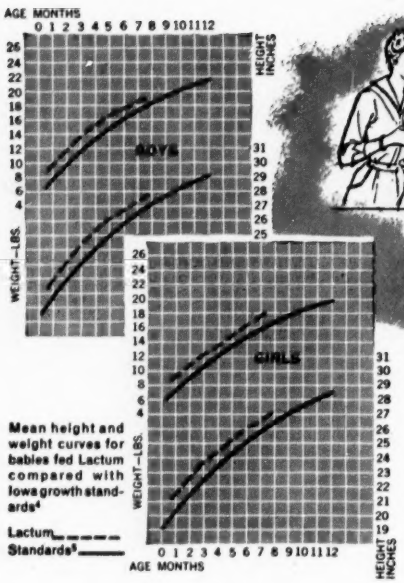
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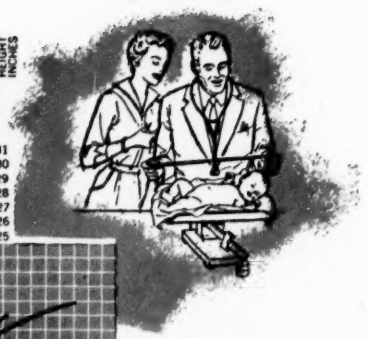

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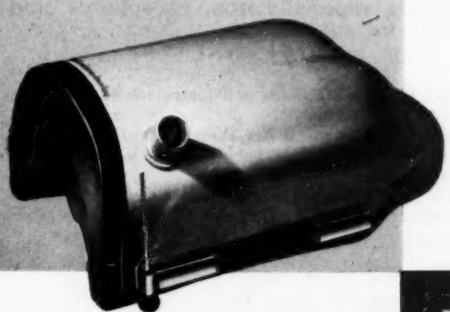

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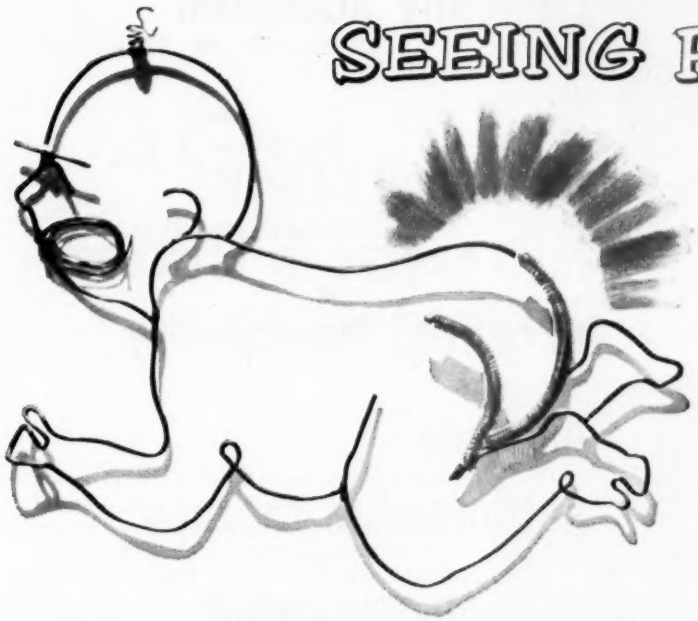

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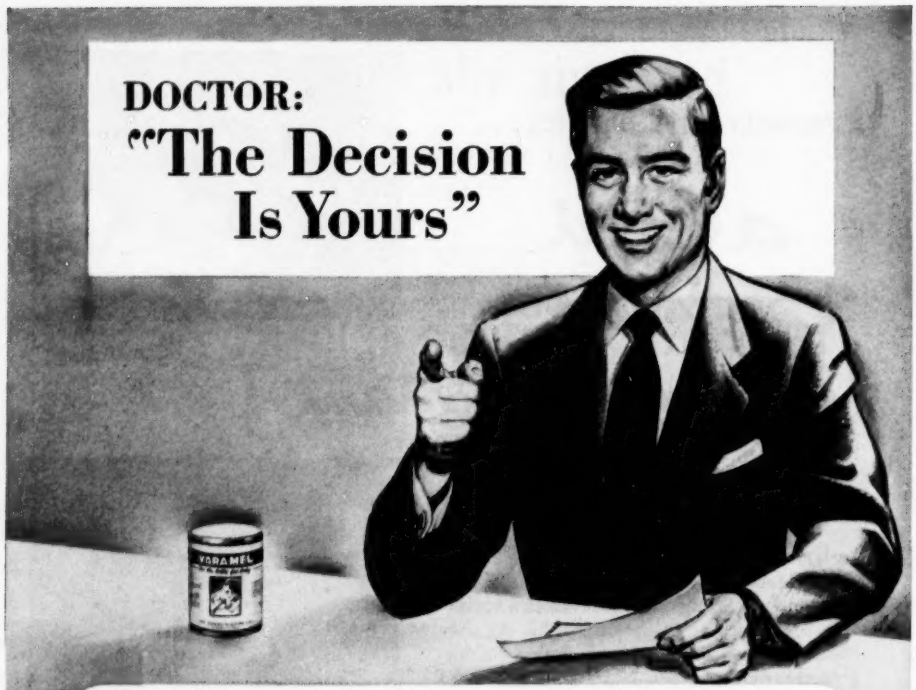

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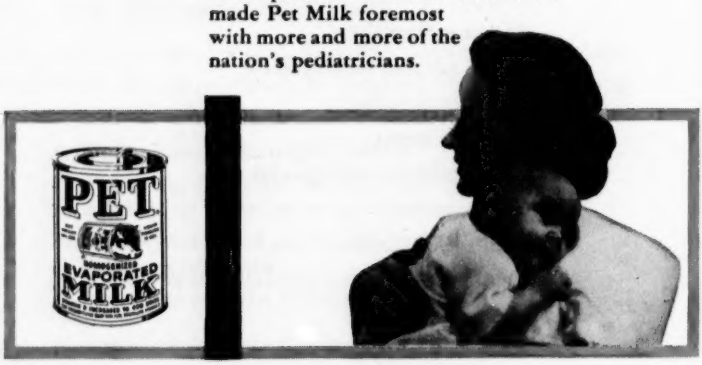

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PROLONGED OBSTRUCTIVE JAUNDICE IN INFANCY

IV. Neonatal Hepatitis

SYDNEY S. GELLIS, M.D.
JOHN M. CRAIG, M.D
AND
DAVID YI-YUNG HSIA, M.D.
BOSTON

IN A PREVIOUS report,[1] we have reviewed the case histories of 156 infants admitted to the Children's Medical Center because of prolonged obstructive jaundice beginning early in life. Although at the time of admission these patients presented a uniform clinical picture and were admitted with a tentative diagnosis of atresia of the bile ducts, further studies revealed that approximately 60% of the cases were due to biliary atresia, 15% of the cases were due to inspissated bile associated with erythroblastosis fetalis and 25% of the cases were considered to be due to inspissated bile of unknown etiology. The last group was characterized by early onset of jaundice during the first few weeks of life, acholic stools, dark urine, and moderate hepatomegaly and splenomegaly. Laboratory studies on these infants [2] showed their urine to contain bile and their stools to be free of both bile and urobilinogen; the flocculation tests of liver function were usually negative. The one-minute and total serum bilirubin were, however, always elevated and showed either a slowly falling or a variable trend. Follow-up studies revealed that about 60% of these infants recovered without sequelae, some developed cirrhosis despite treatment, and a small group died as a result of either cirrhosis or the complications of surgery. It was felt that this condition resulted from several different etiologies, none of which was fully understood, and for this reason, the group was labelled the inspissated bile syndrome of unknown etiology.

In 1952, Craig and Landing,[3] in a study of the pathology material available in this group of infants and additional cases, came to the conclusion that these patients suffered from a viral hepatitis. They found that there was gross distortion of the liver cell cord pattern with great variation in liver cell size. Multinucleate giant parenchymal cells were diffusely distributed throughout the lobules. The findings varied from the classic postmortem lesions described by Lucké [4] and Lucké and Mallory [5] only in the lack of widespread central necrosis and complete destruction of many of the liver cells of the lobule. They concluded that the changes were diagnostic of viral hepatitis during early life.

Earlier, Stokes and his associates [6] had reported a series of cases of 12 infants in whom hepatitis developed during the first two months of life. The pathologic

From the Departments of Pediatrics and Pathology, Harvard Medical School, and the Children's Medical Center.

Aided by grants from the Playtex Park Research Institute and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

findings of six of those who died were similar to those described in older children and adults but with certain peculiar and somewhat specific morphological changes. More recently, Stokes [7] has reported that serum hepatitis virus was apparently transmitted to human volunteers by injection of blood from one of the infants who died and also from his mother.

In view of these reports, it appeared essential to review our cases, and from the history of the mothers and siblings of these infants, to endeavor to determine whether or not viral hepatitis, either of the infectious or homologous serum type, could be shown to be responsible for the disease in these infants.

MATERIALS AND METHODS

A total of 42 infants with the syndrome of inspissated bile of unknown etiology were studied. Twenty-six of these infants were included in the previous report.[1] Sixteen additional infants seen since then were added to make up the present series. The latter group showed all of the clinical and laboratory findings reported in the earlier group. In each infant, hemolytic disease was satisfactorily ruled out by blood-grouping studies.* Atresia of the bile ducts was excluded

TABLE 1.—*Follow-up of Infants with Neonatal Hepatitis*

	Explored Surgically	Not Explored	Total
A. Follow-up complete			
1. Living and well	16	13	29 (71%)
2. Living with jaundice and cirrhosis	3	1	4 (10%)
3. Dead	7	1	8 (19%)
During postoperative period	1		
With cirrhosis	6		
B. No follow-up	1	0	1
Total	27	15	42

by surgical exploration in about two-thirds of the cases and by the disappearance of jaundice, return of bile to the stools, and clinical recovery among the rest.

Three clinical studies were undertaken on these patients and their families: 1. A new follow-up study was carried out to determine the ultimate clinical course of this disease. This was successful in all but one of the infants in the series. 2. The pathology material was reevaluated for evidence of viral hepatitis according to the criteria established by Craig and Landing.[3] 3. The family history of these infants was reexamined. A questionnaire was sent to each family requesting the following information: (*a*) history of jaundice or hepatitis in the mother either prior to or during the pregnancy involving the jaundiced infant; (*b*) history of prolonged jaundice during infancy among siblings older than the jaundiced infant, and (*c*) history of prolonged jaundice among siblings younger than the jaundiced infant.

RESULTS

1. *Follow-up Studies.*—The follow-up data are summarized in Table 1. It was found that 29 of the 41 infants (71%) are living and well. All of these are free from jaundice, are passing normal-colored stools and urine, and have no enlargement of liver or spleen. None of them show any of the stigmata of cirrhosis or portal hypertension.[8] Liver function tests have been repeated on most of the patients, and all are within normal limits. Follow-up has ranged from 6 months to 12 years after recovery.

* Performed at the Blood Grouping Laboratory, Children's Medical Center, by Dr. Louis K. Diamond and Dr. Fred H. Allen Jr.

Four of the 41 infants (10%) are living but are still jaundiced and show evidences of cirrhosis and portal hypertension consisting of hepatomegaly, splenomegaly, ascites, xanthoma, varices, and severe itching. One of these children is over 6 years of age, and the others are all less than 2 years of age. Eight of the 41 infants (19%) have died. Seven of these had undergone exploratory procedures; one died of cholangitis during the immediate postoperative period, while the remaining infants died from two months to two years postoperatively from bleeding esophageal varices and hepatic failure. All those that died continued to be jaundiced up to the time of death. It is of importance to note that the morbidity and mortality was limited almost entirely to the group which had undergone surgical exploration, while the cases treated medically usually made satisfactory recoveries. The higher mortality rate in the group which had undergone surgery could not be explained by the presence of more severe disease inasmuch as severely involved cases and cases of milder degree fell equally into the explored and unexplored groups.

2. *Pathology Material.*—All liver sections were found to be characteristic of viral hepatitis as described by Craig and Landing.[3]

TABLE 2.—*Summary of Survey of Families of Infants with Neonatal Hepatitis*

	No. Persons Surveyed	No. with Jaundice
A. Mothers of infants with neonatal hepatitis	40	1*
B. Siblings of infants with neonatal hepatitis		
1. Older siblings	25	0
2. Twins	1	1*
3. Younger siblings	7	1
Total	33	2 (1*)

* History incomplete.

3. *Family History.*—The survey of the families of these patients is summarized in Table 2. Of the 41 mothers studied, only one had a history of hepatitis. The records did not state whether she had infectious hepatitis or homologous serum hepatitis, nor whether she had hepatitis during pregnancy or preceding it. Unfortunately, it has been impossible to obtain a satisfactory follow-up on this mother.

None of the 25 siblings older than the jaundiced infants studied yielded a history of prolonged jaundice during infancy. The parents of one of the jaundiced infants claimed that the twin brother was jaundiced until three month of age. This was denied by their family physician, and, since this infant was never seen by us, it is difficult to evaluate this case. Of the seven younger siblings of our jaundiced patients, one had a definite history of prolonged jaundice during infancy, as shown below.

REPORT OF CASES

FAMILY A

CASE 1 (#347490).—K. P., a white baby girl, was first admitted to the Children's Medical Center on July 20, 1949, at 4 weeks of age, because of increasing jaundice.

Past history revealed that she was the first child of a healthy 28-year-old woman who had an uneventful pregnancy. Delivery was normal, and the infant weighed 7 lb. 7 oz. (3,370 gm.) at birth. Family history was significant in that neither the mother nor any other members of the family had ever been jaundiced or anemic.

The present illness started on the third day of life, when the infant was noted to be jaundiced for the first time. The jaundice persisted and became severer prior to admission. The stools were light-colored and the urine dark.

Physical examination showed a well-developed and well-nourished active icteric infant. The liver was 3 cm. below the costal margin, and the abdomen appeared moderately rounded.

Laboratory studies showed the urine to contain 2+ bile but no urobilinogen. The stools were clay-colored and free from both bile and urobilinogen. Blood-grouping studies showed the following: The patient was A—, Coombs negative, the father was B+ (Rh_1), probably heterozygous, and the mother was A+. Fragility tests showed hemolysis beginning at 0.40 and completed by 0.34. Liver function tests are summarized in Table 3.

Because of the possibility of biliary atresia, the patient was explored surgically on Sept. 2, 1949. The extrahepatic biliary system was found to be patent, and both saline and dye were injected successfully. The ducts contained yellow thick bile. Liver biopsy was reported as consistent with viral hepatitis with typical giant-cell formation.

TABLE 3.—*Liver Function Tests Performed on Parents and Children in Family A*

Date	Clinical Condition	Thymol Turbidity	Thymol Flocculation	Cephalin-Cholesterol Flocculation	1-Min. Bilirubin	Total Bilirubin
Case 1. (K. P.)						
7/20/49	.....	0.2	0	±	4.3	7.3
8/ 4/49	Postoperative	0.5	0	0	3.5	5.9
8/ 6/49	.....	...	..	..	5.3	9.8
9/22/49	.....	0.5	0	0	2.5	6.2
12/29/49	Cirrhosis	2.2	0	3+	1.2	2.5
3/ 2/50	Decreasing jaundice	1.2	0	0	0.6	1.3
6/ 5/50	Esophageal bleeding	0.2	0	0	0.5	0.9
10/31/50	.....	0.5	0	0	1.1	2.3
Case 2. (P. P.)						
10/19/53	.....	1.0	2+	3+	2.7	5.1
10/27/53	.....	3.0	2+	0	4.3	8.6
11/ 3/53	Cortisone started	1.0	1+	1+	2.0	4.7
11/ 6/53	.....	1.0	1+	1+	5.4	8.8
11/13/53	Cortisone stopped	4.0	0	0	2.7	5.0
11/30/53	.....	...	..	..	1.3	3.2
12/21/53	Jaundice fading	...	..	..	0.9	1.9
Father P.						
10/19/53	.....	1.0	1+	0	0.3	1.0
Mother P.						
10/19/53	.....	1.0	1+	0	.06	0.12
1/18/54	.....	1.0	1+	1+	.2	0.4

Postoperatively, a small amount of bile was found in the stool. Repeat duodenal intubation, however, showed no bile. The child was discharged still jaundiced. During the next year this appeared to diminish somewhat, but signs of cirrhosis developed.

She was readmitted on June 20, 1950, because of bleeding from esophageal varices. At that time, she was questionably jaundiced, the abdomen was distended, the liver was 7 cm. below the costal margin, and the spleen was 6 cm. below the costal margin. It was the opinion of the surgical service that a satisfactory shunt procedure could not be performed.

She was admitted for the third and final time on Feb. 25, 1952, because of hematemesis and melena. Despite transfusions and supportive therapy, she developed pneumococcal peritonitis and died March 16, 1952.

The postmortem diagnosis was as follows: postnecrotic scarring of the liver, generalized icterus, ascites, hepatosplenomegaly, marked esophageal varices, massive GI hemorrhage, multiple hemorrhage infarctions of the liver.

CASE 2 (#406915).—P. P., a white baby girl, sibling of Case 1, was first admitted to the Children's Medical Center on Oct. 19, 1953, at one month of age, because of increasing jaundice.

Past history revealed that pregnancy was complicated by morning sickness and hydramnios. Labor was induced at term, and a 7 lb. 14 oz. (3,570 gm.) normal infant was delivered uneventful-

fully. Scleral icterus was noted on the second day, and at the time of discharge from the hospital, on the seventh day, icterus remained, but the liver was not enlarged. The patient did well at home but passed dark urine and white to yellowish stools. Three days prior to admission, the parents felt that the jaundice was increasing, and the family pediatrician noted hepatosplenomegaly and referred the infant to the Children's Medical Center.

Physical examination showed a well-developed well-nourished icteric infant with a large abdomen. The liver edge was 6 cm. below the costal margin, and the spleen 2 cm. below the costal margin.

Laboratory studies showed the urine to contain 2+ bile and no urobilinogen. The stools were clay-colored, but urobilinogen was present. Duodenal intubation revealed bile to be present. Blood grouping studies showed the patient was AB +, Coombs negative. The liver function tests on the infant and her parents are summarized in Table 3.

The infant was given 100 mg. of cortisone daily by mouth ior five days, which did not affect the course of the disease. She was discharged from the hospital at 2 months of age, still jaundiced. At 6 months of age, she was found to be slightly icteric, with the liver 6 cm. below the costal margin and the spleen 4 cm. below the costal margin. There have been several nosebleeds, and varices have been demonstrated by barium swallow.

COMMENT

In our previous report,[1] we pointed out that the pathogenesis of the syndrome of inspissated bile of unknown etiology was as yet poorly understood. Small bile ducts, hepatic immaturity, and dehydration appeared to play a role in causing biliary stasis and inspissation. However, early congenital cirrhosis of the liver with jaundice, cholangitis, and viral hepatitis could not be ruled out with certainty. The recent findings of Craig and Landing,[3] Stokes and his co-workers,[6] and Schwartz and co-workers [9] strongly suggest that some form of hepatitis, probably viral, is responsible for this syndrome, and the proper name to be applied to the condition appears to be neonatal hepatitis.

If neonatal hepatitis is viral in origin, it is important to determine the nature of the virus and its source. Since infectious hepatitis has been highly prevalent in this community, it should be considered first as a possible etiology. In most of these cases, onset of jaundice was noted during the first or second week of life. Since Colbert [10] has pointed out that the incubation period of infectious hepatitis virus is from 10 to 40 days, with an average of 25 days, it seems unlikely that most of the infants acquired their disease after birth. Furthermore, there were no known cases of hepatitis in the families at the time to serve as contacts, and there is a paucity of cases of infectious hepatitis in infants under 2 years of age both in the literature † and in our own experience,‡ suggesting that very young infants have a high degree of immunity to this disease. Thus it appears probable that the virus was transmitted to the infant across the placental barrier during intrauterine life.

There is little evidence to suggest that the transplacental passage of infectious hepatitis virus is responsible for neonatal hepatitis. Zondek and Bromberg [19] and Hsia, Taylor, and Gellis [20] have shown that infants born of mothers with infectious hepatitis during pregnancy did not develop the disease. Immune antibodies are thought to develop rapidly following the viremia of infectious hepatitis, as suggested by the skin test studies of Stokes,§ making maternal transmission more difficult.

† References 11-16.

‡ References 17 and 18.

§ References 21 and 22.

There is somewhat more evidence to suggest that the virus of homologous serum hepatitis might be responsible for neonatal hepatitis, although this is by no means conclusive at the present time. First, Stokes [7] has successfully transmitted the virus from one such infant and from his mother to human volunteers. This work needs to be confirmed. Second, unlike infection with the virus of infectious hepatitis, most persons do not appear to develop antibodies after exposure to the virus of homologous serum hepatitis,[23] and as a result become silent carriers of the virus.‖ Some of these carriers have a past history of jaundice and hepatitis, but others have negative histories. It is interesting to speculate if any or all of the mothers of these infants might be silent carriers, and it will be important to study their liver functions.

If these mothers are carriers of homologous serum hepatitis virus, one might expect them to transmit the virus across the placental barrier during other successive pregnancies, since the virus has been shown to be present in such carriers for years.[7] This occurred in one of our families, and three other such families with two or more cases of neonatal hepatitis (Case histories summarized in Appendix) have been brought to our attention. Scott and co-workers [26] have recently reported a family in which three fatal cases of hepatitis with jaundice occurred in early infancy. Two other siblings born between the first and second jaundiced patients were apparently unaffected but did have positive cephalin cholesterol flocculation tests. In our series, at least 35 siblings from 25 families did not develop this condition. Seven of these siblings were born subsequent to the birth of the jaundiced infants, a group in which repeat cases would appear most likely. One must therefore conclude that if neonatal hepatitis is due to the transplacental passage of the homologous serum hepatitis virus, it appears unlikely to affect more than one sibling, at least in a clinically recognizable form. Furthermore, in one of the families with two cases of neonatal hepatitis (Family C), the mother had a child without hepatitis between the two infants with neonatal hepatitis. This does not appear to be consistent with the silent carrier state unless the viremia is not constant, the passage of virus is determined by the condition of the placenta, or such mild disease may occur that it gives rise to no signs or symptoms. It is obvious that the etiology of neonatal hepatitis can only be confirmed ultimately by additional virus transmission studies using human volunteers. However, at the present time, the virus of homologous serum hepatitis appears to be the most acceptable cause for this unusual condition, although it is possible that some other virus besides those of infectious and homologous serum hepatitis may eventually be incriminated as the cause of neonatal hepatitis.

At present little is known regarding treatment of neonatal hepatitis. Supportive measures, such as protein infusions, whole blood, vitamins, and an adequate protein intake, are helpful. Surgery should be avoided if biliary atresia can be satisfactorily ruled out without exploration,[2] since the infants do poorly following surgery, perhaps because of the anesthesia and trauma of the surgical exploration. We have recently found oral cortisone useful as a diagnostic and possibly therapeutic tool. Patterson [27] has shown that the hormone acts as an excellent cholagogue. In biliary atresia, the hormone has no effect on the obstructive jaundice, while in neonatal hepatitis, it will frequently dramatically lower the bilirubin level and relieve the obstruction, although its effect on the ultimate course of the disease remains to be determined.¶

‖ References 7, 24, and 25.

¶ Gellis, S. S., and Hsia, D. Y. Y.: Unpublished data.

Although the incidence of recurrence of neonatal hepatitis in subsequent pregnancies is low, and the value of gamma globulin in the prevention of homologous serum hepatitis appears doubtful,[23] the use of gamma globulin should nevertheless be seriously considered in these mothers during subsequent pregnancies. If given, 0.1 cc. per pound (0.5 kg.) of body weight should be administered intramuscularly every six to eight weeks during the entire pregnancy.

SUMMARY

A group of 42 infants with the syndrome of inspissated bile of unknown etiology has been further reviewed and found to have neonatal hepatitis.

Although the condition occurred in two siblings in one family, the siblings of the other infants appeared to be free of jaundice and hepatitis and are well.

On the basis of the present available evidence, it would appear that the virus of homologous serum hepatitis is the most likely cause of neonatal hepatitis and is transmitted across the placental barrier by mothers who are silent carriers of the virus.

The possibility that other viruses may be the cause of neonatal hepatitis has not been excluded.

APPENDIX

The following additional cases of neonatal hepatitis occurring among siblings have come to our attention.#

FAMILY B

CASE 1.—At the age of 2 months, this infant had a bout of rather severe diarrhea, during which jaundice developed accompanied by dark urine and clay-colored stools. This jaundice persisted intermittently until 13 months of age, when the child was admitted to the Buffalo Children's Hospital.

Physical examination showed a jaundiced infant, with the liver 5 cm. below the costal margin and the spleen 6 to 7 cm. below the left costal margin. Laboratory studies showed the urine to contain bile and no urobilinogen. The stools were positive for urobilinogen. Chemistries showed the cephalin-cholesterol flocculation test to be 4+; the bilirubin was 9.2 mg. per 100 cc.

On the 10th hospital day, exploratory laparotomy was undertaken, and the biliary tree was found to be patent, although the spleen and liver were found to be enlarged. Postoperatively, the patency of the biliary tree was confirmed by cholangiogram, and the stools became dark in color.

Subsequently, a punch biopsy revealed a healing hepatitis and early cirrhosis. The infant was still mildly icteric when last seen.

CASE 2.—P. L., a sibling of Case 1, was well until 5 months of age, when his mother noted the gradual onset of jaundice. At the time, he ran a low-grade fever but was otherwise well. He did not respond to a regimen of low-fat-high-protein diet, and jaundice persisted so that at the age of 15 months he was admitted to the Buffalo Children's Hospital because of recurrent bouts of severe epistaxis.

Physical examination showed a deeply jaundiced infant with a distended abdomen. The liver was 2½ fingers below the costal margin and the spleen 1.5 cm. below the costal margin.

On the fourth day after admission, he developed a massive hematemesis and went into shock. Despite therapy with whole blood, he died on the same day.

Autopsy showed cirrhosis of the liver, apparently on the basis of chronic viral hepatitis with secondary splenomegaly, portal obstruction with ascites, and marked dilatation of the esophageal veins with massive hemorrhage into the stomach and small intestines.

Case reports of Family B were furnished by Dr. Mitchell Rubin, Children's Hospital, Buffalo, and of Family C, by Dr. John J. Ryan, 17 Prospect St., Waltham, Mass.

It is difficult to be certain whether Case 2 represents neonatal hepatitis or hepatitis acquired after birth. However, the connection is sufficiently unusual to be worthy of inclusion.

Family C

Case 1.—In 1949, following the birth of a normal infant in 1946, this infant developed jaundice and liver disease and died at 6 weeks of age. Autopsy showed the liver to be completely regenerating after almost total necrosis. The pathologist felt that the etiology lay between chemical necrosis and virus hepatitis, with the comparative absence of an inflammation favoring the former. There was no evidence of congenital malformation of the liver.

Subsequently, the mother gave birth to a child who developed hydrocephalus but did not have jaundice or hepatitis.

Case 2.—M. J. W., a sibling of Case 1, developed diarrhea and vomiting at 2 months of age. This was treated successfully with changing the feedings, but on the next day he developed a shocklike state and became jaundiced for the first time.

Physical examination showed a normal infant with the liver 1.5 cm. below the costal margin; the spleen was not palpable. Laboratory studies showed the serum bilirubin to be 4.7 mg. per 100 cc., the cephalin-cholesterol flocculation test to be 4+, the alkaline phosphatase to be 15. The total protein was 3.5 gm. per 100 cc., with the albumin 2.7 gm.

Two days later, the pulse and temperature rose, and the abdomen became distended. Despite all types of supportive therapy, the infant died on the eighth day of illness.

Autopsy showed changes in the liver consistent with neonatal hepatitis.

Family D

This family was cited by Moncrieff.[28] A trained nurse developed infectious hepatitis in 1944 and made an uneventful recovery. Subsequently, she married, and in 1949 gave birth to a baby boy who was quite severely jaundiced for some time after birth and eventually recovered, although it was left with an enlarged firm liver which is almost certainly cirrhotic. Two years after the birth of the first child, another boy was born, who also became jaundiced and died. Autopsy showed a classic picture of hepatitis.

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SYMPTOMS OF ASCARIASIS, WITH SPECIAL REFERENCE TO CONVULSIONS

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AMONG THE hardy perennials of maternal folklore is the belief that worms cause fits. In giving the history of a child's epilepsy, many mothers tell of giving vermifuges in an effort to exorcise the worms thought to be responsible for the seizures. There is little accurate information available on the subject of convulsions in cases of ascariasis.

Occasional reports of convulsions as a symptom of Ascaris lumbricoides infestation occur in the literature. Worth [1] described several cases of febrile convulsions which he ascribed to worms. Carver [2] described two similar cases. Grant [3] remarked that Ascaris was thought to produce fever and convulsions in India. Wilkinson [4] described a case of epileptiform convulsions in a child with worms and remarked that fever and convulsions were a well-recognized result of worms "among the poorer classes." Duprey [5] described a fatal case of an 8-year-old boy who died after having several convulsions, which he ascribed to the toxins of Ascaris found in the lower bowel at autopsy. He remarked that such complications of Ascaris infestation were frequent in the West Indies. Keller [6] maintained that convulsions were no commoner in the group of 167 Tennessee children he studied than in a control group and stated that there is no constant clinical manifestation of ascariasis. Belding [7] mentioned convulsions as a possible reflex nervous symptom of ascariasis, and Osler [8] mentioned convulsions as a possible irritative manifestation. Einhorn, Miller, and Whittier [9] described convulsions as a symptom of Ascaris infection in 4 out of a group of 125 children studied in Panama. Swartzwelder [10] mentioned convulsions in 23 out of a group of 202 cases of ascariasis in New Orleans. Studying the possible association between convulsions and Ascaris infestation from a different viewpoint, Bridge [11] found 9 cases of ascariasis among a group of 742 epileptic children, remarking that any effect of the worms on the epilepsy was most likely through the depletion of the child's general health rather than through any direct action of the parasite or its ova on the child's brain.

In order to get more definite data on the incidence of convulsions in children infested by A. lumbricoides, a study was made of 200 consecutive cases of proved ascariasis in children seen at the Johns Hopkins Hospital. Of these 200 children, the greatest number were in the preschool age group, with over half being less than 4 years of age, the maximal incidence of ascariasis being at the age of 3. There were about twice as many white as Negro children in the group. The majority (119 cases) were underweight. It is uncertain whether this poor nutritional status was the result

of the infestation, or whether a preexisting dietary inadequacy made the children more susceptible to infestation, as adequate nutrition is an important factor in immunity.[12] The majority of these 200 children passed worms without any history of febrile disturbance, although 32 passed worms during or just after a fever, and 2 passed them after surgical operations. Almost half of the 200 children had no apparent symptoms or signs before passing worms. The number of symptoms reported by the mother in each case varied with her intelligence, interest, ability to observe, and state of emotional stability, but the most frequent symptom mentioned was occasional abdominal pain, with anorexia the next most common symptom (Table 1).

TABLE 1.—*Symptoms Seen in Children Before Passing Worms*

No symptoms	82
Occasional abdominal pain	44
Poor appetite	34
Restless sleep	23
Convulsions	17
Vomiting	18
Failure to gain weight	13
Fretful behavior	10
Nervousness	8
Protruding abdomen	7
Constipation	7
Pallor	6
Nose-picking	6
Apathy, listlessness, laziness	5
Diarrhea	5
Cough	5
Teeth-grinding	5
Enuresis	4
Headache	4
Weakness	3
Dirt-eating	3
Excessive appetite	2
Occasional nausea	2
Occasional back pain	2
Easy fatigability	1
Occasional fever	1
Blood-streaked stool	1
Pain on defacation	1
Urinary frequency	1

Most of these 200 children were found on examination to be free from evidence of other disease, but about one-third of them had concurrent abnormalities of various sorts, of which mediastinal tuberculosis was the most common (Table 2).

Of the 200 cases of ascariasis, convulsions were reported in 17. This incidence of 8.5% is considerably above the usually accepted incidence of epilepsy in the general population, which is usually considered to be 0.3% [13] or 0.4%.[11] It is also higher than the 1.5% incidence of epilepsy among all pediatric patients at the Johns Hopkins Hospital, as well as higher than the 4 to 5% among all pediatric patients having a history of some form of convulsive disorder.[11] However, a close study of these 17 cases of ascariasis with a history of convulsions shows that all but two patients had had epileptic seizures for months or years and continued to have them long after the worms were removed. One of these died in status epilepticus a year after the elimination of his worms, and autopsy showed no recurrence of ascariasis.

Several showed evidences of epileptic mental deterioration. Only 2 of the 17 patients having convulsions accompanying ascariasis had an acute convulsive history of only one or two days, and both of them had no more convulsions after the worms were eliminated. This suggests that the ascariasis was merely an incidental finding in 15 epileptic children who had convulsions for many months before and after their Ascaris episodes. The remaining 2 out of 200 Ascaris-infested children had acute convulsive episodes that might be an evidence of cerebral irritation due to the presence of the worms or their toxins. Unfortunately, no electroencephalographic studies of these two children were made. Neither of them had fever at the time of examination, and their mothers did not know whether they were febrile before the convulsions. One was a 7-year-old child who had had right-sided Jacksonian seizures for

TABLE 2.—*Other Disease Found on Examination*

Mediastinal tuberculosis	12
Mental retardation	7
Rickets	6
Otitis media	6
Pneumonia	4
Tonsillitis	4
Pharyngitis	4
Rheumatic fever	3
Meningitis	3
Urinary tract infection	2
Impetigo	2
Cervical adenitis	2
Congenital syphilis	2
Typhoid	1
Erysipelas	1
Lymphangitis of leg	1
Chicken pox	1
Megacolon	1
Eczema	1
Scarlet fever	1
Jaundice	1
Diabetes	1
Hepatomegaly	1
Postinfluenzal encephalitis	1

two days before being brought to the hospital, each preceded by a brief aura of nausea. He had passed several worms by bowel recently, had Ascaris ova in his stool and 5% eosinophilia in his blood, and had no more evidence of either worms or convulsions after treatment with chenopodium and santonin. The other child was 2 years old and had had several generalized convulsions for one day before being brought to the hospital, with vomiting of several Ascaris worms. There was no recurrence of either worms or convulsions after treatment with santonin.

If the 15 children who had typical epileptic seizures for years before and after their episode of Ascaris infestation are eliminated, it leaves only 2 out of 200 whose acute convulsive disorder could be reasonably suspected of being due to Ascaris infestation. This 1% incidence of convulsions as a possible symptom of ascariasis is certainly no more than would be expected in the general population,[11] and it lends support to Keller's assertion [6] that convulsions are no more common in children with ascariasis than in any other group of children.

CONCLUSIONS

In a study of 200 children with proved ascariasis, 17 (8.5%) had a history of convulsions, but only 2 of these (1%) had acute convulsive disorders that did not persist for long intervals before and after the episode of ascariasis. This suggests that convulsions due to ascariasis do not occur any more often than convulsive disorders in the general population.

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CASE-FINDING OF HANDICAPPED CHILDREN, WITH SPECIAL REFERENCE TO CEREBRAL PALSY

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ONE OF THE problems in the administration of a program for handicapped children is that of early case-finding, e. g., how to find as early as possible those children who are in need of accurate diagnosis and prompt and maximum treatment and rehabilitation of a higher caliber. It is apparent that if handicapped children are to be absorbed into the regular community as quickly as possible, early case-finding is the first step for them and their families. That early case-finding is a problem in the case of cerebral palsied children is attested by the fact that of the 346 children with cerebral palsy reported to the Bureau of Handicapped Children in 1952 only, (0.9%) were reported during the first year of life and only 129 (37%) in the age group of one to four years.

In the case of children with cerebral palsy, there are certain known or suspected facts in the etiology which should be of epidemiological significance in early case-finding. These facts should be able to lead us to the more "vulnerable" groups of children in whom cerebral palsy is more likely to occur: those children born prematurely; those delivered by high forceps, midforceps, breech, or Caesarean section; those delivered in the course of abnormal labor (prolonged, difficult, or precipitate); those born of mothers who have had certain complications (placenta previa, premature separation of the placenta, toxemia, etc.), and those reported to have certain birth injuries or congenital malformations. This report describes a follow-up four years after birth of children born in New York in 1948 who were reported on the live-birth certificates to have had certain birth injuries or congenital malformations.

METHOD OF STUDY AND FOLLOW-UP

The following method of study and follow-up was used in 1952 on the group of babies reported born alive in 1948 in New York:

1. The live-birth certificates of all babies reported in 1948 to have had a congenital malformation or birth injury were reviewed. There was a total of 1,825 children with a reported congenital malformation and/or birth injury.

From the Bureau for Handicapped Children and the Bureau of Records and Statistics, New York City Department of Health.

United Cerebral Palsy of New York City, Inc., assisted in this study.

2. From this review, 253 children were selected for the follow-up. Those children selected for follow-up included all those reported with any of the following conditions: intracranial hemorrhage, possible intracranial hemorrhage, intracranial injury, possible intracranial injury, fractured skull, severe molding of the head, forceps mark or injury to the head, laceration of the head or face, impacted or injured shoulders, asphyxia or anoxia, cyanosis, atelectasis, other respiratory difficulty (including the need for resuscitation), hemolytic disease, and other conditions suggestive of possible central nervous system injury.

Name of child_____ Date of birth_____

Address_____ Certificate No._____

TO BE FILLED IN BY PARENT OR GUARDIAN

1. Place of birth_____ Name of physician who delivered child_____ Address_____
2. Does your child now have any physical defects? If yes, please describe.
   - Difficulty in walking. ☐ No ☐ Yes_____
   - Difficulty in sitting up. ☐ No ☐ Yes_____
   - Difficulty in feeding. ☐ No ☐ Yes_____
   - Difficulty in using hands. ☐ No ☐ Yes_____
   - Difficulty in speech ☐ No ☐ Yes_____
   - Difficulty in seeing. ☐ No ☐ Yes_____
   - Difficulty in hearing. ☐ No ☐ Yes_____
   - Convulsions, fits, or loss of consciousness. ☐ No ☐ Yes_____
   - Other. ☐ No ☐ Yes_____
3. Has your child ever had any of the above handicaps?
   ☐ No ☐ Yes If yes, describe_____
4. At what age did your child first begin to:
   - Sit up_____
   - Stand_____
   - Walk_____
   - Talk_____
5. Does your child have any special problems? ☐ No ☐ Yes If yes, describe_____
6. If your child has a handicap, would you like any assistance from the Bureau for Handicapped Children? ☐ No ☐ Yes
7. Is your child now under the care of a physician or hospital? ☐ No ☐ Yes If yes, state name and address_____
   - Name of parent or guardian_____
   - Address_____

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Questionnaire sent to parents of children with congenital malformations or birth injuries.

3. A search was made in 1952 for death certificates in the group of 253 children selected from the 1948 live-birth certificates. A total of 86 infant death certificates was found filed with the Department of Health.

4. For the remaining 167 children, a simple questionnaire was drawn up and sent twice to the parents in 1952 at their 1948 home address. This questionnaire (Figure) asked for information on certain symptoms, such as difficulty in sitting, walking, feeding, seeing, hearing, and speech, convulsions, data on gross growth and development, and their status regarding current medical care. The parents of 54 children responded to the questionnaire; in this group there were 3 children reported to have died during the four-year period whose death certificates had not been previously found.

TABLE 1.—*Response to Follow-up and Outcome by Reported Birth Injury or Congenital Malformation*

Birth Certificate Report	Total No.	Response to Follow-Up						Outcome					
		Death Certif.	Parents' Reply	PHN Visits	Known to BHC Only	No Information	Info. Available, %	Dead	Normal	Handicapped	Unknown	Dead, %	Handicapped, %
Severe molding	15	1	6	..	1	7	53.3	1	5	2	7	6.7	13.3
Cyanosis	24	3	8	4	..	9	62.5	5	9	1	9	20.8	4.2
Atelectasis	22	10	2	3	..	7	68.2	13	1	1	7	59.1	4.5
Hemolytic disease	19	12	..	2	..	5	73.7	12	2	..	5	63.2	0.0
Respiratory difficulty	19	4	2	5	1	7	63.2	7	4	1	7	36.8	5.3
Hydrocephalus	32	24	2	3	..	3	90.6	27	1	1	3	84.4	3.1
Possible hydrocephalus	4	..	..	1	..	3	25.0	..	1	..	3	0.0	0.0
Cerebral hemorrhage	6	3	2	..	..	1	83.3	3	2	..	1	50.0	0.0
Possible cerebral hemorrhage	15	7	3	..	..	5	66.7	7	3	..	5	46.7	0.0
Cranial injury	9	4	2	..	..	3	66.7	4	1	1	3	44.4	11.1
Possible cranial injury	24	6	8	3	..	7	70.8	7	7	3	7	29.2	12.5
Fractured skull	4	..	3	..	..	1	75.0	..	3	..	1	0.0	0.0
Hematoma of head, face, or scalp	9	1	2	3	..	3	66.7	1	5	..	3	11.1	0.0
Forceps mark	6	..	2	2	..	2	66.7	..	2	2	2	0.0	33.3
Laceration of head	7	1	2	1	..	3	57.1	1	3	..	3	14.3	0.0
Other head injury	8	2	3	1	..	2	75.0	2	4	..	2	25.0	0.0
Anoxia	10	5	3	2	..	..	100.0	7	2	1	..	70.0	10.0
Shoulder injury	7	..	1	2	..	4	42.9	..	2	1	4	0.0	14.3
Miscellaneous	13	3	3	1	1	5	61.5	3	3	2	5	23.1	15.4
Totals	253	86	54	33	3	77	69.6	100	60	16	77	39.5	6.3

5. For the remaining 113 children, a similar questionnaire was used in 1952 by a public health nurse who visited the home. By means of this home visit, 33 children were found; in this group were 11 reported to have died during the four-year period whose death certificates had not been previously found.

6. The records of the Bureau for Handicapped Children were searched for any information concerning the entire group of 253 children. Six of the group had been known to the bureau because of some handicap; with three of these no contact had been possible by public health nurse and no response was received from the parents.

7. Where there was known to be a private physician or hospital caring for a handicapped child in the group, a report was secured from the physician or the hospital.

RESULTS

Response to Follow-up.—Follow-up information was available on 176 children (70%) at the end of this four-year period. The degree of response to the follow-up for the various diagnostic categories varied from 100% for children reported with anoxia to 25% for children reported at birth with possible hydrocephalus (Table 1). The response to the parents' questionnaire (54, or 21% of the total group of 253

TABLE 2.—*Status of Child by Type of Response to Follow-up*

Status	Total		Death Certif.		Parents' Reply		PHN Visits		Known to BHC Only		No information	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	60	23.7	..	....	41	75.9	19	57.6	..	....	..	....
Handicapped	16	6.3	..	....	10	18.5	3	9.1	3	100.0	..	....
Deaths	100	39.5	86	100.0	3	5.6	11	33.3	..	....	..	....
No information	77	30.5	..	....	..	....	..	....	..	....	77	100.0
Total	253	100.0	86	100.0	54	100.0	33	100.0	3	100.0	77	100.0

children) consisted of 76% normal children, 19% handicapped children, and 6% deaths. The response to the public health nursing visits to the home (33, or 13% of the total group of 253 children) consisted of 58% normal children, 33% deaths, and 9% handicapped children. The essential differences between these two responses indicate that parents were more likely to reply to the questionnaire if they had a handicapped child and less likely to do so if their child had died (Table 2).

Outcome.—For the entire group of 253 children, 100 (40%) had been known to have died during the four-year period of follow-up, 60 (24%) were normal, and 16 (6%) were handicapped. No information could be obtained on 77 children (30%). This information on outcome means that this group had a minimum infant mortality rate of 395 per 1,000 live births, which is 16 times that for the city as a whole. It also means that the handicapping rate in the group is at least 63 per 1,000 live births (Table 1).

The range of mortality in the group varied from a high of 84% for those children reported at birth to have had hydrocephalus to a low of 0.0% for those children reported at birth to have had fractured skull, possible hydrocephalus, forceps mark on the head, or a shoulder injury. The rate of handicapping varied from a high of 33% in the group reported at birth with forceps marks to a low of 0.0% in the group with hemolytic disease, possible hydrocephalus, cerebral hemorrhage, possible cerebral hemorrhage, fractured skull, hematoma of the head or face, laceration of the head, or other head injury (Table 1).

TABLE 3.—*Information on Handicapped Group*

Case No.	Birth Wt., Lb.-Oz. (Gm.)	Type of Delivery	Congenital Malformation Reported	Birth Injury Reported	Source	Known to BHC	Diagnosis	Degree of Handicap	Was Child Under Current Medical Care?	Source of Medical Care	Handicaps
1	9- 2 (4,139)	Spontaneous vertex	.....	Cerebral damage	Parents, CP school unit	Yes	Cerebral palsy, athetoid	Severe	Yes	Hospital, CP clinic	Difficulty in walking, feeding, using hands
2	7- 6 (3,345)	Midforceps	.....	Cerebral edema, forceps mark on temple	Parents	No	Cerebral palsy, spastic	Severe	Yes	Nursery in country	Blind; unable to walk, sit up, feed, use hands, or talk; has had two convulsions
3	7-12 (3,515)	Midforceps	.....	Difficult delivery, severe molding	BHC and orthopedist	Yes	Cerebral palsy, hemiplegia	Moderate	?	2 qualified orthopedists	Involvement of leg and arm
4	8- 7 (3,827)	Low forceps	.....	Labored respiration	BHC	Yes	Cerebral palsy, spastic quadriplegia	Severe	Yes	Hospital, CP clinic, and convalescent home	Difficulty in sitting, speech, and walking
5	4-11 (2,162)	Spontaneous vertex	Prematurity, atelectasis	.....	Parents, PH nurse	No	Hydrocephalus	Severe	No	Qualified pediatrician, and neurological hospital	Delayed development; unable to walk alone; has large head and strabismus; had convulsions first week after birth
6	8- 6 (3,799)	Low forceps	Hydrocephalus	.....	Parents	No	Hydrocephalus	Severe	Yes	GP	Mentally retarded; cannot sit or walk; has had convulsions
7	5- 6 (2,438)	Spontaneous breech	.....	Anoxic damage, cyanotic; resuscitation for 30 min.	Parents, PH nurse	No	Mental retardation	Moderate	No	.....	Slow mentally; did not begin to speak until the age of 4 yr.
8	7- 9 (3,430)	Low forceps	.....	Large caput, duecedaneum forceps bruise over face and scalp	Parents, PH nurse, hospital report	No	Facial paralysis, birth injury of brain	Moderate	Yes	Hospital clinic	Mentally slow; has had convulsions; has difficulty in walking; does not talk well
9	7- 2 (3,232)	Low forceps	.....	Possible cerebral injury	Parents, PH nurse, hospital reports	No	Congenital dislocation of hip, pes planus	Slight	No	Hospital clinic	Malposition of feet and difficulty in walking
10	9- 0 (4,082)	Spontaneous vertex	.....	Possible cerebral damage	Parents, PH nurse	No	Possible arm injury	Moderate	No	Hospital clinic	Unable to use one arm
11	3- 3 (1,440)	Spontaneous vertex	Clubfoot	Cyanotic	Parents, hospital report, BHC	Yes, for club foot	Clubfoot, optic atrophy, nystagmus, strabismus	Moderate	Yes	Hospital clinic	Difficulty in seeing
12	Not stated	Spontaneous vertex	.....	Cerebral edema due to marked molding	Parents and physician	No	Febrile convulsions	None	Yes	GP	Has had two convulsions associated with fever
13	9-13 (4,451)	Low forceps	.....	Impacted shoulders, fractured humerus	PH nurse, hospital report	No	Genu valgum, scoliosis, birth trauma to shoulder, pronated feet	Moderate	Yes	Hospital clinic	Some difficulty with feet
14	8-14 (4,026)	Low forceps	.....	Forceps bruise on side of head and neck	PH nurse, hospital report	No	Strabismus, speech defect	Slight	Yes	Hospital clinic	Speech and vision
15	8- 6 (3,799)	Spontaneous breech	.....	Possible Erb's paralysis	PH nurse	No	Bilateral overlapping toe	Slight	Yes	Qualified orthopedist	Foot—slight
16	.....	.....	.....	.....	BHC	Yes	Achondroplasia, cleft palate, clubfeet, hernia	Severe	Yes	Hospital	Severe; died at age of 1 yr. 4 mo. in hospital

Type of Handicap.—Information about the handicapped group is given in Table 3. Of the total of 16 children reported to be handicapped at the age of 4 years, 4 had cerebral palsy (Cases 1 to 4), one (Case 8) probably had cerebral palsy, although he was reported with a tentative diagnosis of brain injury and facial paralysis, 2 had hydrocephalus (Cases 5 and 6), and 1 was mentally retarded (Case 7). Of the other eight children, seven had a variety of orthopedic or neurological conditions, and the remaining one a serious visual defect. Of the entire group of 16 handicapped children, all had a handicap which was probably related to prenatal and natal influences. Five of the 16 children were reported to have had at least one convulsion during the four-year period. Of the 16 handicapped children, 11 were under current medical care, 4 were not under current medical care, and for the remaining child, the status of medical care was unknown. With the exception of two children under the care of a physician in general practice (one child had hydrocephalus and the other child had febrile convulsions) and one child with mental retardation who had never been under medical care, all the children had been under competent medical care (Table 3).

TABLE 4.—*Period of Gestation*

Period, Wk.	Normal		Handicapped		Death		No Information		Totals
	No.	%	No.	%	No.	%	No.	%	No.
22-26	..	..	..	..	5	5	1	1	6
27-28	1	2	..	..	..	..	..	..	1
29-30	..	..	..	..	7	7	..	..	7
31-34	..	..	1	6	11	11	3	4	15
35-38	13	22	3	19	17	17	5	7	38
39-42	43	72	12	75	57	57	61	79	173
43 and over	1	2	..	..	..	..	5	7	6
Full term	..	..	..	..	2	2	1	1	3
9th mo.	..	..	..	..	1	1	..	..	1
Not stated	2	3	..	..	..	..	1	1	3
Totals	60	100	16	100	100	100	77	100	253

Of the group of 16 handicapped children, only 5 had been known previously to the Bureau for Handicapped Children. The incompleteness of voluntary reporting of handicapped children to a crippled children's agency is illustrated.

The fact that four children with definite cerebral palsy and a fifth child with probable cerebral palsy were found means an incidence of 19.8 per 1,000 live births in this group. This incidence is eight times that found by Phelps [1] (2.5 per 1,000 live births) and 3.4 times that found by Levin and Brightman [2] in the Schenectady, N. Y., study (5.9 per 1,000 live births). In addition to these four children with cerebral palsy found at the age of 4 to 5 years, two additional children with cerebral palsy had died prior to the conduction of the study, one at the age of 4¼ years, the other at less than 1 year of age.

SOME CHARACTERISTICS OF THE CHILDREN

Because of the probable relationship between perinatal factors and certain handicapping conditions, a further analysis of the most important of these factors was undertaken. That period of gestation is a factor is shown in Table 4. The group of children who subsequently died had the highest percentage of short gestation. The

death group also had the highest percentage of abnormal pregnancies (Table 5). The most frequent types of complications of pregnancy included eclampsia and preeclampsia, placenta previa, vaginal bleeding, and the Rh factor. Because of the small number of cases, no relationship of death and handicapping condition could

TABLE 5.—*Status of Pregnancy*

Status	Total	Normal Group		Handicapped Group		Death Group		No Information	
		No.	%	No.	%	No.	%	No.	%
Normal	188	48	80	14	88	66	66	60	78
Not normal	64	12	20	2	12	34	34	16	21
Not stated	1	..	..	..	..	..	..	1	1
Totals	253	60	100	16	100	100	100	77	100

TABLE 6.—*Type of Delivery*

Type	Normal Group		Handicapped Group		Death Group		No Information		Totals	
	No.	%	No.	%	No.	%	No.	%	No.	%
Spontaneous vertex	18	22.8	5	6.3	25	31.7	31	39.2	79	100.0
Low forceps	19	31.1	6	9.9	15	24.6	21	34.4	61	100.0
Midforceps	12	32.4	3	8.2	11	29.7	11	29.7	37	100.0
High forceps	1	50.0	..	0.0	..	0.0	1	50.0	2	100.0
Spont. and assisted breech	2	18.2	..	0.0	7	63.6	2	18.2	11	100.0
Breech extraction	2	8.7	..	0.0	15	65.2	6	26.1	23	100.0
Version and breech extraction	..	0.0	..	0.0	4	100.0	..	0.0	4	100.0
Caesarean section	4	13.3	2	6.7	19	63.3	5	16.7	30	100.0
Puncture of head	..	0.0	..	0.0	2	100.0	..	0.0	2	100.0
Unknown	2	50.0	..	0.0	2	50.0	..	0.0	4	100.0
Totals	60	23.8	16	6.3	100	39.5	77	30.4	253	100.0

TABLE 7.—*Birth Weight*

Birth Weight, Gm.	Normal		Handicapped		Deaths		No Information	
	No.	%	No.	%	No.	%	No.	%
1,000 or less	..	....	..	....	4	4.0	1	1.3
1,001-1,500	1	1.7	1	6.2	2	2.0	..	....
1,501-2,000	..	....	..	....	6	6.0	4	5.2
2,001-2,500	1	1.7	1	6.2	18	18.0	5	6.5
2,501-3,000	16	26.6	1	6.2	10	10.0	18	23.4
3,001-3,500	25	41.6	3	18.9	19	20.0	21	27.3
3,501-4,000	9	15.0	4	25.0	18	12.0	14	18.2
4,001-4,500	4	6.5	4	25.0	7	7.0	5	6.5
4,501-5,000	1	1.7	..	....	3	3.0	2	2.6
Over 5,000	..	....	..	....	1	1.0	1	1.3
Not stated	3	5.2	2	12.5	17	17.0	6	7.7
Totals	60	100.0	16	100.0	105	100.0	77	100.0

be demonstrated with parity of the mother. In this series delivery by Caesarean section, spontaneous breech, and breech extraction had the highest percentage of deaths where the numbers were large enough to be of statistical significance (Table 6). In this series no relationship between length of labor and outcome to the child could be demonstrated. Place of delivery and type of accoucheur appear to be less

important factors in this study. In regard to birth weight, 30% of the death group weighed 2,500 gm. or less at birth, in contrast to 3.4% of the normal group of children (Table 7). No relationship could be found between the presence of a handicapping condition and any of these factors; the need of further study with a larger series of cases is indicated.

COMMENT

This study, although some of the numbers in the subgroups are relatively small, would tend to indicate that a follow-up of babies with reported birth injuries and congenital malformations is productive from the viewpoint of case-finding of handicapped children and of giving assistance to them and their families. Despite the fact that the relationship between factors such as birth weight, period of gestation, complications of pregnancy, length of labor, and Caesarean section and handicapping conditions has not been statistically validated in this study, additional studies of these factors may provide further leads in case-finding.

For a number of years, New York has had a "newborn plan" in which public health nurses of both the official and the voluntary health agencies have visited the home of selected newborn infants. Priority for visiting has been as follows: (1) premature infants; (2) midwife deliveries; (3) babies born out of wedlock; (4) ward-born babies. On Jan. 1, 1952, an additional group of newborn infants was included in this public health nursing home visiting program—babies with birth injuries or congenital malformations reported on the live-birth certificates. This program is now in the process of being evaluated, but it would appear from this study that the selection of the congenital malformation and birth injury group was a wise one.

Although it would be desirable to have a 100% follow-up on any group because of the need for complete data, a follow-up response of 70% over a four-pear period may be considered quite good and adequate. The loss of the 30% was due directly to the fact that in a large urban area families move reasonably frequently, and it is usually difficult to trace them. It is, of course, likely that the shorter the period selected for follow-up, the more complete would be the response. The 4-year-old group was selected because it was felt that by the age of 4 years many handicapping conditions associated with the birth process should have been detected and diagnosed.

It would appear desirable to enlarge the scope of the perinatal problem from the present one of fetal and neonatal deaths to include those handicapping conditions which may be thought traceable to prenatal and natal causes. In other words, it is not enough to deliver a live baby, but the perinatal area should be enlarged to include morbidity which may be related to obstetric factors, i.e., those damaged or handicapped children with conditions related to the birth process. This is particularly important because many physicians who do obstetrics do not, as a general rule, render long-term health supervision to the babies they have delivered. Thus, they may be deprived of this type of follow-up information which might be of importance to them and their future obstetric patients.

The fact that only 6 of the total 16 handicapped children (only four of the six with cerebral palsy) were known to the Bureau for Handicapped Children would

appear to demonstrate the limitations of a crippled children's program maintaining a register of all handicapped children in a community. However, many more studies are necessary before such a conclusion may be definitely drawn.

It is hoped that the information derived from this study may be of assistance to practicing physicians who are responsible for the delivering and for the health supervision and care of children, to those public health personnel interested in the care of handicapped children, and to those responsible for programs of public health nursing home visiting of newborn infants.

SUMMARY

A follow-up study was done in 1952 on those children reported in 1948 on the live-birth certificates to have had selected birth injuries or congenital malformations. Of the 253 children, 100 (40%) had died; 60 (24%) were normal, 16 (6%) were handicapped, and 77 (30%) could not be located at the end of this four-year period. The infant mortality rate of 395 per 1,000 live births in the group was 16 times that of the city as a whole, and the handicapping rate was 63 per 1,000 live births. Of the 16 handicapped children found, 4 were definitely known to have cerebral palsy, and a fifth child probably had the same diagnosis, resulting in a cerebral palsy incidence in the total group of 19.8 per 1,000 live births. The implications of these findings are discussed.

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ABO HETEROSPECIFIC PREGNANCY AND HEMOLYTIC DISEASE

A Study of Normal and Pathologic Variants

III. Hematologic Findings and Erythrocyte Survival in Normal Infants

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THIS PAPER is concerned with the clinical and hematologic appraisal of unselected infants who were products of homospecific and heterospecific pregnancies. The isoantibody patterns in the cord bloods of these infants and in the sera of their mothers have been described in the two preceding sections. The report is divided into a clinical and an experimental study. The first part contains observations on the physical findings, blood picture, and bilirubin levels of the newborn infants. It is followed by a comparative study of the behavior of transfused donor erythrocytes, compatible and incompatible with the maternal blood group, in healthy babies resulting from homospecific and heterospecific pregnancies.

A. CLINICAL AND HEMATOLOGIC DATA

Methods.—The cord bloods were collected by members of the obstetrical service in the delivery room by allowing blood from the placenta immediately after ligation of the umbilical cord to drip by gravity into serological test tubes containing dried Wintrobe oxalate mixture. The cord had first been allowed to pulsate for several minutes. The tubes were quickly rotated and placed in the refrigerator until the hemoglobin and red cell count determinations could be made, usually within 18 hours.

For the determination blood was withdrawn with calibrated pipettes after careful mixing of the sample, and the oxyhemoglobin was determined in an Evelyn photoelectric colorimeter. Red blood cell counts were made for check purposes only from the same specimens in the standard manner, using only one pipette for each sample. The bilirubin concentration was determined in the serum obtained in a simultaneously collected sample of cord blood which was allowed to clot. White blood cell counts and differential counts were done only occasionally, but films were always made.

At 3 to 4 days of age hemoglobin and red blood cell counts were determined on capillary blood obtained from heel pricks, and at this time blood smears were also made. Additional blood was collected in a capillary tube for a second bilirubin determination. The bilirubin method was a micromodification of the Evelyn-Malloy method.[1]

At approximately 21 days, during a home visit by a field worker, another capillary sample of blood was obtained for hemoglobin and red blood cell count.

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Observations.—With respect to their clinical behavior, no difference could be observed between the 92 infants of homospecific and the 112 infants of heterospecific pregnancies. On examination at birth and at the time of discharge, on the third to fifth days, no abnormalities such as splenomegaly, hepatomegaly, or pallor were noted in any case. The degree of jaundice was difficult to appraise, since 90% of the infants were Negroes. However, in no instance was clinical jaundice evident in the first 24 hours. In those infants who became jaundiced in the following days, the degree of icterus did not seem excessive in any case. The few premature infants in the group showed no peculiarities other than those accounted for by their prematurity.

The values for the hemoglobin levels of the cord blood were available in 55 cases of homospecific pregnancy, in 30 cases of O-A heterospecific pregnancy, in 32 cases of O-B heterospecific pregnancy, and in 9 cases of mixed heterospecific A-B or B-A pregnancy. The frequent occurrence of clotting in the oxalated samples of cord blood, in spite of every reasonable precaution, accounted for the loss of a substantial number of specimens in each group. Samples of capillary blood taken three days post partum were available from 86 infants of Group O, 44 of Group A, 54 of Group B, and 17 of the mixed group. Table 1 shows the averages, medians, and ranges of the hemoglobin determinations for the four groups.

The average and median values for the hemoglobin concentration in the cord bloods were low in all groups, as compared to the normal values obtained by Mollison and Walker.[2] No claim is made here for the validity of our results in terms of absolute values. Under the conditions of the study the collection of cord bloods had to be carried out by personnel not directly under our supervision, and sampling errors might have escaped detection. For purposes of comparison between the several groups of infants, however, the possible error was disregarded, since it should affect the results in each group in the same manner. The relative validity of the cord-blood hemoglobin levels was borne out by the fact that on the third day the hemoglobin levels of infants with low initial values were found to be of the same order as those of the infants with adequate initial levels in each of the groups studied. Under these assumptions no significant differences could be shown between homospecific and heterospecific pregnancy as far as the cord hemoglobin concentration was concerned.

The capillary hemoglobin levels on the third day were not subject to the potential sampling errors of the cord specimens. Though there was a difference of 5.6% in the means between O-O and O-A groups, the O-B group showed a mean value slightly greater than the O-O group. When O-A and O-B groups were combined and the mean of 16.6 was compared with that of the homospecific group, the difference was definitely below the level of significance, 1.8%. The values at 21 days showed the same lack of significant differences.

The averages of bilirubin values of the cord bloods were slightly higher in the O-A group than the O-O group and still higher in the O-B group. The combined average of the two heterospecific groups was 1.24 mg. per 100 cc., or 8.8% above the average for the O infants. The range and distribution of the values was uniform (Table 2) but, for the size of the sample, the difference cannot be regarded as significant. The observed difference coincides, however, with the figure obtained in a much larger sample by Rosenfield.[3]

The values for serum bilirubin obtained at 3 days of age showed a much less uniform distribution in all groups (Table 3). In occasional cases in each group, bilirubinemia of unexpected intensity with values above 12 mg. was encountered.

TABLE 1.—*Hemoglobin and Bilirubin Values of Infants of Homospecific and Heterospecific Pregnancies*

	Homospecific	Heterospecific		
		Mother O		Mother A or B
	Mother O Infant O	Infant A	Infant B	Infant B or A
Cord hemoglobin				
No. cases	55	30	32	9
Range	11.1-17.8	10.7-23.3	9.8-17.8	11.3-16.0
Mean	14.5	14.5	14.3	13.4
Median	14.7	14.3	14.7	13.0
3-day hemoglobin				
No. cases	86	44	54	17
Range	12.5-21.9	12.0-21.2	12.6-21.9	12.0-21.9
Mean	16.9	16.0	17.1	17.3
Median	16.9	16.1	16.9	17.3
21-day hemoglobin				
No. cases	92	49	60	19
Range	9.8-18.3	9.8-19.4	9.0-17.3	9.8-19.4
Mean	13.9	13.2	13.4	14.5
Median	13.7	13.0	13.7	14.2
Cord bilirubin				
No. cases	74	50	51	17
Range	0.44-2.19	0.48-2.20	0.33-2.70	0.5-1.7
Mean	1.15	1.20	1.29	1.1
Median	1.08	1.19	1.13	1.0
3-day bilirubin				
No. cases	58	34	44	16
Range	0.30-15.0	0.4-15.9	0.30-19.0	0.7-13.0
Mean	4.75	5.42	4.91	4.3
Median	4.00	5.00	4.0	3.9
Cord bilirubins				
Term	O-O/O-A = 0.664	O-O/O-B = 1.685		O-O/OA + OB = 1.294
Premature	O-O/O-A = 0.509	O-O/O-B = 0.996		O-O/OA + OB = 0.199
3-day bilirubins				
Term	O-O/O-A = 0.594	O-O/O-B = 0.625		O-O/OA + OB = 0.266
Premature	O-O/O-A = 0.555	O-O/O-B = 0.9		O-O/OA + OB = 0.790

TABLE 2.—*Distribution of Serum Bilirubin Concentrations in Cord Bloods*

Mg./100 Cc.	Mother O Infant O No. of Cases	Mother O Infant A No. of Cases	Mother O Infant B No. of Cases	Mother A or B Infant B or A No. of Cases
0.21-0.40	0	0	2	0
0.41-0.60	3	5	3	1
0.61-0.80	11	4	3	2
0.81-1.00	18	7	8	6
1.01-1.20	17	13	14	2
1.21-1.40	10	7	4	4
1.41-1.60	6	7	4	1
1.61-1.80	4	2	4	1
1.81-2.00	1	1	5	0
2.01-2.20	4	4	2	0
2.21-2.40	0	0	0	0
2.41-2.80	0	0	2	0
Total	74	50	51	17

The Group A and B infants of O mothers did not, with one single exception, show abnormal hemoglobin values or clinical evidence of hemolytic disease. In the case of a Group B infant (No. 345) the cord bilirubin had been 0.98 mg. At 3 days of age, the bilirubin had risen to 19.7 mg. per 100 cc., though the hemoglobin was 16.4, and the child appeared otherwise well. There was no free anti-B antibody in the cord serum, nor was the maternal antibody pattern unusual in any way. In a second infant of the same group the bilirubin rose from 2.7 mg. at birth to 18.0 at 3 days of age. Again, neither the fetal nor the maternal antibodies were remarkable, and the infant had a hemoglobin of 15.5 gm. at 3 days of age and appeared well. Among the Group A infants of O mothers three had bilirubin values exceeding 12 mg. per 100 cc. at 3 days of age. In all three cases the maternal antibody pattern was average. Only one of the three infants exhibited a mild anemia, with cord and three-day hemoglobin values of 13.7 gm. No free antibody was found in the infant's plasma.

TABLE 3.—*Distribution of Serum Bilirubins at Three Days of Age*

Mg./100 Cc.	Mother O Infant O No. of Cases	Mother O Infant A No. of Cases	Mother O Infant B No. of Cases	Mother A or B Infant B or A No. of Cases
0.0-1.0	11	8	9	3
1.1-2.0	6	7	4	5
2.1-3.0	4	4	4	2
3.1-4.0	9	2	5	2
4.1-5.0	2	1	4	2
5.1-6.0	4	3	3	1
6.1-7.0	6	2	4	0
7.1-8.0	5	3	3	0
8.1-9.0	5	3	2	0
9.1-10.0	1	2	2	0
10.1-11.0	1	0	2	0
11.1-12.0	2	1	0	0
12.1-13.0	0	0	0	1
13.1-14.0	1	1	0	0
14.1-15.0	1	1	0	0
>15.1	0	1	2	0
Total	58	34	44	16

Two of the Group O infants likewise had unexpectedly high bilirubin levels at 3 days of age, 13.1 and 15.2 mg. per 100 cc., without accompanying anemia and without obvious cause. All infants whose bilirubin values are tabulated in Tables 1, 2, and 3 were full-term babies. One must conclude that in some infants, independent of blood-group factors, the excretion of bilirubin is handled less efficiently than in the majority. Yet, the bilirubin values of the third day of life, like those of the cord blood, showed slightly higher averages and medians in the heterospecific Groups O-A and O-B than in the homospecific Group O-O. The small group of cases of mixed heterospecific pregnancies, on the other hand, showed values at or below those for the homospecific group.

No studies of erythrocyte fragility were made, but blood films from the three-day samples were carefully scrutinized for the presence of spherocytes, since spherocytosis had been reported as a frequent finding in ABO hemolytic disease.[4] Definite spherocytosis could not be demonstrated in any of the infants, regardless of the fetal-maternal blood-group combinations. No late anemias were encountered in the examinations made three weeks after birth.

Comment.—The observations presented above may be summarized by stating that in more than 100 unselected consecutively studied infants resulting from pregnancies heterospecific in the O-A-B system, no clear-cut evidence of a physiologic disadvantage as compared with a similar homospecific group could be demonstrated by means of clinical appraisal, hemoglobin determinations, or search for spherocytes. No instances of early icterus were observed in the present series. Admitting the technical difficulties in recognizing mild icterus in Negro infants, the cord bilirubin values were within normal range for all groups. The slightly higher means and medians of the bilirubin values both at birth and at 3 days of age are suggestive of a handicap to the infant in heterospecific pregnancy of the type mother O, infant A or B. If larger series of observations should prove this trend, it should be emphasized that surely this handicap is without physiologic importance, at least in the full-term infant. None of these babies developed neurologic complications or significant degrees of anemia. Insofar as they were clinically apparently well babies, the absence of abnormal serologic patterns in the maternal or fetal sera appears significant.

Halbrecht [5] observed icterus precox, a term coined by him to describe icterus in less than 24 hours, in 90 infants from among 16,000 deliveries and calculated an incidence of 1 in 180 births. He noted that 95% of the cases occurred in heterospecific pregnancies and further calculated an incidence of one case of icterus precox for every 25 heterospecific births. This high incidence does not appear in smaller consecutively studied series of unselected infants such as the present study or the series of Bryce and her associates.[6] The occurrence of early icterus or other signs or symptoms attributable to maternal-fetal O-A-B incompatibility would therefore always appear to be a pathologic event, though not necessarily serious in its implications.

The Australian authors [6] observed a difference of 9% in the hemoglobin values of capillary blood on the first day of life, as well as in subsequent examinations of the infants' blood, between the means for homospecific and heterospecific babies, favoring the homospecific group. They found no comparable differences in red cell counts, however. No divergence between compatible and incompatible groups was found by Potter and Bernstein [7] or by us. The 2 gm. difference in the averages between A secretors and nonsecretors deserves further investigation but cannot be regarded as significant at present.

B. ERYTHROCYTE SURVIVAL STUDIES

In hemolytic disease of the newborn due to Rh incompatibility, the demonstration of maternal antibody attached to fetal erythrocytes by means of the antiglobulin test furnished direct and final proof of the immune mechanism by which the fetal cells are affected. In establishing the concept of ABO hemolytic disease on a similar basis, two main difficulties arose. First, the "natural" isoagglutinins of the mother were present by definition in every heterospecific pregnancy and could not be used to prove a pathologic mechanism occurring only in a small proportion of cases. This difficulty was only partly overcome by the demonstration of high maternal anti-A or -B agglutinin titers, since a simple quantitative relationship could not be established. The characterization of isoantibodies with so-called immune characteristics

in the maternal serum by several authors * clarified the situation somewhat but not completely. Second, the antiglobulin test, for reasons still poorly understood, failed in the hands of most workers to show sensitization of fetal A or B cells by maternal antibody, thereby leaving a seemingly vital gap in the theory of ABO hemolytic disease. The most direct and most convincing proof that maternal anti-A or -B antibodies can damage fetal erythrocytes of the corresponding blood group was furnished by the erythrocyte survival studies of Boorman, Dodd, and Trinick [10] and of Mollison and Cutbush.[11] These authors showed that when infants thought to suffer from ABO hemolytic disease were given simultaneous transfusions of labeled A and O erythrocytes, the cells of the A donor were eliminated more rapidly than were

TABLE 4.—*Data on Infant Recipients and Donors of Survival Study of Dual Cell Population*

			First Transfusion			Second Transfusion			Inagglutinated Cells			
									Pretransfusion		Post-Transfusion	
Case	Mother	Infant Recipient	Day	Amount, Cc.	Type Donor Blood	Day	Amount, Cc.	Type Donor Blood	Anti-A or B Serum	Anti-M Serum	Anti-A or B Serum	Anti-M Serum
1	A_1MeDE	A_1MCde Secretor BW, 6 lb. (2,720 gm.)	2	30	A_1Nede	3	30	OMede	68,000	3,000	211,000	366,000
2	$A_1BMNcDE$	A_1MCDE Nonsecretor BW, 5 lb. 10 oz. (2,550 gm.)	7	50	A_1NcDe	8	30	OMN D	1,000	2,000	437,000	370,000
3	OMNcDe	A_1MNcDE Nonsecretor BW, 5 lb. 15 oz. (2,690 gm.)	2	30	A_1NcDe	3	30	OMN D	6,000	1,000	223,000	375,000
4	OMede	BMeDe Nonsecretor BW, 7 lb. (3,175 gm.)	2	30	BNCDe	3	40	OMN D	38,000	1,000	210,000	422,000
5	OMN D	A_1MNcDE Nonsecretor BW, 7 lb.	4	25	OMN D	5	25	A_1Nede	21,000	2,000	115,000	195,000
6	ONcDe	A_1MNcDE Secretor BW, 4 lb. 5 oz. (1,960 gm.)	2	20	OMN D	3	30	A_1N D	16,000	2,000	290,000	660,000
7	OMNcDe	BMNcDE Secretor BW, 7 lb.	3	35	BNCDE	4	35	OMNcDe	10,000	3,000	145,000	290,000

those of the O donor. These experiments were limited to one infant for each group of investigators and have not been repeated to our knowledge. It was thought worth while to extend the observations of the British workers and to study the survival of simultaneously transfused O and A or B cell population in presumably healthy infants, as well as in cases of hemolytic disease.

Material and Methods.—The selection of the infants was governed entirely by the maternal-fetal blood-group combinations and by the likelihood of cooperation from the parents in serial examinations. On these grounds five infants were selected from the group of heterospecific pregnancies referred to in the first two communications of this series. In addition, two newborn infants referred to our hospital for minor surgical conditions and found by us to be offspring of homospecific pregnancies were included for control purposes. None of the seven infants had clinical evidence of hemolytic disease. One infant was prematurely born, with a birth weight of 4 lb. 5 oz. (1,960 gm.); the remainder were full-term infants.

*References 8 and 9.

The donors were healthy adult volunteers. The blood for transfusion was carefully drawn into sterile flasks containing appropriate minimal amounts of 3% sodium citrate solution. Whole blood was always used in preference to cell suspensions, in order to exclude as much as possible physical trauma to the erythrocytes prior to administration. In the case of O donors, AB group substances were added in order to neutralize the isoagglutinins, the titer of which had been determined previously. The blood was administered within 24 hours after it was drawn, except in one case in which it had been preserved in the refrigerator for three days.

The ABO, MN, and Rh types of donors and recipients were determined, using the techniques previously specified. In addition to the regular cross-matching procedure, the indirect Coombs test was performed in each case, using the infant recipient's serum and the adult donor's erythrocytes. The results were negative in each case.

The infants ranged from 2 to 7 days in age (Table 4). No attempt was made to compensate by preliminary bleeding for the transient increase in blood volume or the polyerythema resulting from the transfusion. The blood was given cautiously into a scalp vein by the drip method or by direct injection from a syringe. The amounts varied from 20 to 50 cc. for a single transfusion. As a rule, the amounts of O and A blood were equal. The two transfusions administered to each infant were performed on two consecutive days. The order in which O and either A or B blood was given varied for technical reasons over which we had no control, but it did not seem to affect the results, probably because only O donors with low isoagglutinin titers were used, neutralizing substance was added, and the dilution of the O plasma in the infant's blood volume was considerable. In no case was there any clinical or laboratory evidence of a reaction to the transfusions. The total red blood cell counts and hemoglobin levels of the infants were followed simultaneously with the differential agglutination studies and showed no undue fall in any case.

The modification of the Ashby differential hemagglutination method used in this study has been described by us previously.[12] The donor A cells used were A_1N and the B cells, BN, identified by their failure to be agglutinated by a highly potent anti-M serum. The inagglutinable count of the recipient's own M erythrocytes after exposure to this serum was always less than 5,000. For the identification of the transfused O cells, a reconstituted powdered rabbit anti-A serum and a liquid anti-B serum, both of high potency, were used. These sera had been used in this laboratory for differential agglutination for several years and had given very satisfactory inagglutinable cell counts in A and B persons. In one instance (Case 2), a 1:1 dilution of the anti-A serum was found to give optimal counts and was used for each consecutive determination. No corrections were made for expanding blood volume, since this factor obviously affected both the transfused O and A cell populations equally.

Observations.—The survival curves of the simultaneously transfused A and O erythrocytes in two infants of the homospecific pregnancy group showed good parallelism, indicating an approximately equal rate of destruction in the circulation of the recipients (Chart 1). Case 1 was the A_1 infant of an A_1 mother, Case 2, the A_1 infant of an A_1B mother. The details for these and the following cases are given in Table 4. One of the infants proved to be a secretor, the other, a nonsecretor.

Heterospecific pregnancies were investigated in three cases of O-A and two cases of O-B maternal-fetal combinations. In one A and one B infant the curves (Chart 2, Cases 3 and 4) for the two donor cell populations were parallel and conformed to those obtained in the homospecific group. In a second A infant (Chart 2, Case 5) the curves were parallel but showed increased elimination of both A and O donor cells. In the third A (Chart 3, Case 6) and the remaining B (Chart 3, Case 7) infant the curves showed a significant divergence, in each case the donated O cells showing greater survival than the A or B cells, respectively.

Of the five infants in the heterospecific group, two were secretors, the remaining three, nonsecretors for their respective blood groups. The two secretors proved to be the A and the B recipients in whom the survival of the homologous donor cells

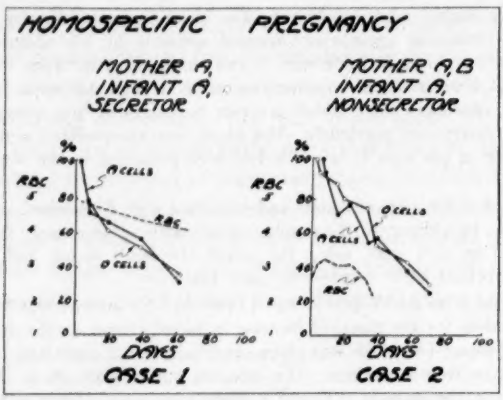

Chart 1

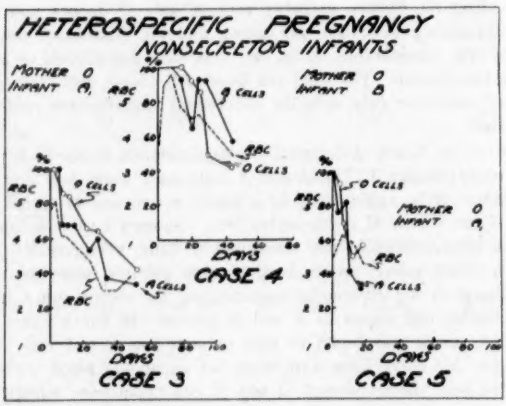

Chart 2

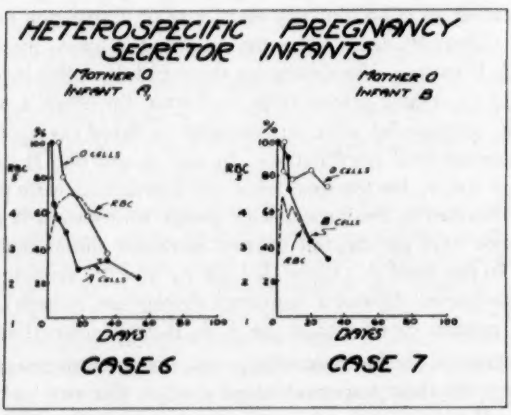

Chart 3

was shortened as compared to that of the O donor cells. At the time of birth the maternal sera had shown no unusual anti-A or -B saline titers and had given negative Witebsky tests. The infants' cord bloods had shown a negative Coombs test and no demonstrable free antibody effective against their own blood group.

COMMENT

The clinical and hematologic observations presented in the first part of this paper, like those of other investigators, failed to indicate a physiologic handicap imposed by heterospecific pregnancy per se. The shortened survival of A or B donor cells as compared to simultaneously transfused O cells in apparently normal infants suggests that subtle mechanisms may exist in heterospecific pregnancy which the conventional serologic and hematologic methods fail to show.

The Ashby method of studying erythrocyte survival is fraught with difficulties which make caution necessary in generalizing from a small number of observations.

TABLE 5.—*Serial Inagglutinable Cell Counts of Normal Newborn Infants Not Given Transfusions and of Adult Controls Inagglutinable Cell Counts*

Case	Mother	Infant	Birth	Day of Life	Inagglutinable Cell Counts	
					No.	Normal Adult Control
1	A	A	Full term	2	27,000	1,500
				10	18,750	1,250
				19	14,500	1,250
				31	6,700	3,200
2	O	B	Full term	3	31,500	3,000
				17	44,000	5,500
				32	18,000	5,500
3	AB	A	Premature	4	17,000	3,750
				12	18,750	2,500
				32	23,000	5,250
4	O	A	Full term	1	52,500	2,000
				20	42,250	1,250
				40	31,000	1,750

The difficulties are especially great in applying the method to newborn infants because of the relatively low sensitivity of the recipients' own erythrocytes to the α and β agglutinins, a fact which could profoundly influence results obtained by counting unagglutinated cells. Mollison,[9] in discussing this technical problem, stated that MN and Rh sera are preferable for differential agglutination of newborn erythrocytes, since the corresponding antigens are fully developed at birth. However, with the Rh sera available to us satisfactory results could not be obtained. The anti-M serum used in this study gave highly satisfactory results in the identification of the transfused AN or BN cells. The A and B sera used to differentiate O cells from the recipients' erythrocytes were of high potency, as shown by the preliminary unagglutinable cell counts in the range of less than 5,000 for adult cells. The higher counts encountered in the newborn reflect the characteristically lower agglutinability of newborn blood but do not invalidate the post-transfusion counts of unagglutinated donor cells. First, the increment following the transfusion of O cells was so substantial that errors due to inagglutinable cells of the A or B recipients would be negligible. In the two cases where divergence of transfused O- and A-cell survival

was observed and where the error might therefore be pertinent as a possible cause for elevating the inagglutinable count interpreted as O cells, the maximum error possible was well below 10%. Second, the agglutinability of newborn A or B cells appears to be relatively constant for each person, or actually to increase somewhat during the first few weeks. Table 5 gives pertinent figures on serially obtained inagglutinable cell counts of four normal infants not given transfusions and adult controls. Thus consecutive inagglutinable counts would conceal an increasingly smaller proportion of recipient A or B cells and therefore become an increasingly reliable index of the donor O cells present. The error would therefore remain either the same or become progressively smaller and would not produce an unduly high count of O donor cells in the later determinations. Third, for each of the sera, anti-A or -B and the anti-M, the initial post-transfusion count was taken as the 100% value on each curve. The comparative sensitivity of the newborn A, B, and M agglutinogens therefore does not directly influence the relationship of the curves. Finally, the expected parallelism between O-cell and A-cell curves in the compatible, AA and AB-A, homospecific infants was actually observed, showing that the possible error inherent in the use of anti-A or -B sera need not be significant.

The total red blood cell counts of the infants were raised to somewhat unphysiologic levels by the experimental transfusions, but this factor would apply equally to all cases and should not produce any differences observed between O- and A-cell survival. In all cases a rapid readjustment of the total red blood cell count took place, so that at 6 weeks of age the values were comparable to those in normal infants not given transfusions. The question as to whether this relatively rapid fall was due to expanding blood volume for which no corrections were made or to hemolytic mechanisms affecting all three cell populations, the recipients' own and those of the two donors, was not investigated. Pertinent only for the problem under study was the fact that the total red blood cell counts behaved similarly in those infants with divergent survival of A and O cells and in those with parallel curves.

The possibility that the increased destruction of one of two simultaneously introduced populations of donor cells was due to the presence of undetected antibodies not related to A and B but effective against Rh or some rare antigen was carefully excluded by the negative indirect Coombs test of the maternal sera and the cross match with the indirect Coombs test between the infant's serum and the cells of both donors in each case.

Accepting the validity of the data obtained under the conditions described, one may conclude that in seemingly normal infants A or B cells may be eliminated somewhat more rapidly than O cells. The phenomenon was limited to infants born of heterospecific pregnancy but was observed in only two infants of that group who happened to be secretors. This result was not anticipated, since the secretor status of the infants had not been considered in the selection of the cases suitable for erythrocyte survival studies. From the small number of cases no conclusions regarding the significance of the secretor status can be drawn. The reason why the secretor infant might destroy donor blood of the homologous group and therefore probably its own blood at an increased rate is obscure. It is apparent that secretor infants act as a better antigenic stimulus for the maternal production of antibodies, and the observations cited in an earlier paper showed this to be true. However, a measurable rise in antibodies after secretor-heterospecific pregnancies was limited to the postpartum period in the entire group, as well as in those infants in whom survival of A or B

cells was shortened. At the time of delivery the maternal sera showed no unusual patterns, and no anti-A or -B antibody could be demonstrated in the infants' cord sera.

The evidence presented in the preceding paper, to the effect that antibody antagonistic to the infant's blood group passes the placenta in every heterospecific pregnancy but is neutralized by the tissue antigen of the fetus, might explain the increased destruction of fetal erythrocytes even in the absence of manifest disease or unusual maternal antibodies. The fixation of antibodies by the tissues does not explain, however, why red cell injury should occur in secretors rather than nonsecretors. If anything, the red cells of secretors should be better protected by the circulating free group substances. As a matter of pure speculation, the thought might be considered that in secretors some of the maternal antibody is loosely bound to the water-soluble group substances in the body fluids and tissues. When released, such antibody might injure the red corpuscles. In normal nonsecretors all maternal antibody specific for the infant's blood group may be presumed to be tightly bound by the water-insoluble group-specific substances of the tissues and not easily released. In this manner the nonsecretor would be more effectively protected.

The conclusions of Boorman and her associates and of Mollison and Cutbush, that the more rapid fall of red cells of the infant's own blood group than of O cells in infants with hemolytic disease due to ABO incompatibility prove the effect of maternal (α or β) isoantibodies on the fetal erythrocytes, are not invalidated by these findings. On the contrary, it becomes apparent that such an effect, though of less degree, may occur not only under pathologic conditions but in seemingly physiologic pregnancies as well.

SUMMARY

Infants born as the result of hemospecific and heterospecific pregnancies were compared with respect to the occurrence of early icterus, bilirubin levels of cord blood and serum on the third day of life, hemoglobin levels, spherocytosis, incidence of splenomegaly or hepatomegaly, and general clincal behavior. No appreciable differences were apparent between the two groups, except for a slightly higher average of the bilirubin levels of questionable significance in the O-A and O-B heterospecific group. The incidence of icterus precox in a random series of 131 infants of heterospecific pregnancies was zero. It was concluded that heterospecific pregnancy per se does not constitute a physiologic handicap to the infant if the usual clinical, hematologic, and biochemical standards are applied. When heterospecific pregnancy is associated with symptoms in the infant which can be attributed to the effects of maternal α or β antibodies, the event is always a pathological one, whether it be benign or serious. With a physiologic measurement the survival of simultaneously transfused O and A or B cells, however, selectively increased destruction of those erythrocytes which are agglutinable by the maternal α or β antibodies can be demonstrated in seemingly normal heterospecific infants whose mothers had no unusual serologic patterns at the time of delivery. This phenomenon was encountered only in secretor infants.

The observed facts suggest that maternal isoantibodies may produce effects on the fetal red cells without clinically or serologically recognizable disturbances in the physiology of the newborn.

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ABO HETEROSPECIFIC PREGNANCY AND HEMOLYTIC DISEASE

A Study of Normal and Pathologic Variants
IV. Pathologic Variants

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ON THE BASIS of a large unselected case material, an attempt was made in the preceding papers * to draw the picture of ABO heterospecific pregnancy as it is ordinarily seen and to describe the effects on the isoantibody patterns of mother and child, as well as on the clinical and hematologic condition of the newborn infant. Against this background, the present study attempts similarly to characterize the pathologic variants of ABO heterospecific pregnancy and to offer observations which may aid in an understanding of the etiology and pathogenesis of ABO hemolytic disease. The case material presented for this purpose, in contrast to that of the earlier studies, was selected in the sense that it consisted only of infants suspected for some reason of having hemolytic disease of the newborn due to ABO incompatibility. All cases of hemolytic disease of the newborn due to maternal isoimmunization against Rh or rare antigens were excluded. All other cases were included without further selection, regardless of the indications for the original referral. The 74 cases thus studied formed the "pediatric group" referred to in the earlier papers. The group was heterogeneous in that not all cases could be classified as ABO hemolytic disease, but homogeneous in that all cases were studied with the same techniques and by the same personnel concurrently with the cases of the "obstetrical group." † In some instances an alternate diagnosis was already suspected or soon became apparent on further examination. Some of the infants proved to be compatible with their mothers in the ABO system. Others, though incompatible, had to be regarded as entirely normal. In still others a satisfactory explanation of the clinical picture was never reached when all diagnostic procedures had been exhausted. The correlations which emerged in the various categories of cases between clinical findings, blood groups, and serologic observa-

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* References 1-3.

† References 1-3.

tions seemed of sufficient diagnostic interest to warrant the presentation of the entire material. It seemed profitable to group the cases in the following manner:

Group I: All cases in which jaundice was the symptom of concern and in which a plausible diagnosis other than possible ABO incompatibility could not be reached. This group was somewhat arbitrarily subdivided as follows.

A. Thirty-eight cases with onset of icterus reported on the first day of life.

B. Six cases in which the onset was delayed or unknown but the icterus was severe or prolonged.

Group II: Ten cases of icterus in the newborn period attributable to causes other than ABO incompatibility but studied in the same manner.

Group III: Seven cases studied for indications arising in the blood-grouping laboratory either because the mother was reported to be Rh negative or because unusual α or β antibodies were found in the maternal serum.

Group IV: Thirteen cases referred for miscellaneous reasons, chiefly anemia in the newborn period.

OBSERVATIONS

Group I A (Early Icterus)

Clinical Features.—The common denominator of this group was the appearance of icterus not otherwise accounted for on the first day of life. Because of this feature this group was chosen as the model with which to compare the other categories, since the early appearance of icterus seemed to be a definitely abnormal occurrence and promised to give the best correlations between clinical and serologic findings. The patients were all full-term infants, and the birth histories were not remarkable. More than one-quarter of the babies were Negroes. Icterus was often reported at birth or immediately afterwards. In some instances the vernix caseosa had been bile-stained. The degree of bilirubinemia at the time of admission was usually but not always well above the range observed in the obstetrical control group.[8] Table 1 shows the observed peak levels of serum bilirubin and the minimum concentrations of hemoglobin in the capillary blood of the patients and summarizes other pertinent clinical and hematologic features. There was a high incidence of anemia, which generally proved to be moderate or mild, never approaching the extreme degrees often seen in infants with severe Rh hemolytic disease. The marked reticulocytosis present in the majority of cases indicated, however, that a hemolytic process of some intensity was taking place but was masked by compensatory hematopoietic efforts. A number of infants also showed marked normoblastemia. More or less marked spherocytosis was observed in nearly all cases in which this feature was studied. Hepatomegaly was usually slight, and splenomegaly was often absent and when present was rarely marked. The majority of the patients were active and vigorous, nursed well, had supple extremities and normal newborn reflexes, and showed no signs of involvement of the nervous system.

The intensity of the jaundice frequently seemed to be greater than the appraisal of the hemolytic process would lead one to expect, but in the majority of cases the icterus cleared rapidly, sometimes by the third or fourth day of life, usually toward the end of the first week, even though the hemoglobin levels might continue to fall for several weeks. In several cases, however, the jaundice increased rather than decreased during the first week, and in one infant the so-called inspissated bile syndrome developed with features of biliary obstruction, such as a rising fraction of direct-reacting bilirubin, acholic stools, and bile appearing in the urine. Several

infants became somewhat lethargic but recovered. In 4 of the 38 patients of Group I A symptoms indicative of the kernicterus syndrome developed between the third and sixth days. These infants were among the more deeply jaundiced infants in the group, though others equally icteric seemed to escape neurologic involvement. Two of the infants showing signs of kernicterus during life died and were found to have the typical gross yellow staining of the cerebral nuclei at autopsy (Cases 8 and 35). One of the survivors (Case 15) died of intercurrent disease at 6 weeks of age, another (Case 4) was reexamined at 8 months of age and appeared grossly retarded. In one additional infant (Case 30), no symptoms indicative of kernicterus were recognized in the newborn period, but at the age of 2 years the infant exhibited ataxia, athetoid movements, and mental retardation.

A general picture resembling that frequently seen in severe Rh hemolytic disease and characterized by a combination of marked visceromegaly, instability of thermoregulation, respiratory and circulatory difficulties, anemia of threatening proportions, and an appearance suggesting "toxicity" was seen only once, in an infant who died without clinical or pathologic evidence of kernicterus on the third day (Case 12). At autopsy the significant findings were pulmonary edema, hemosiderosis, and hematopoiesis in the enlarged liver and spleen.

Two infants exhibited mild edema of the face and extremities but did not seem seriously affected and recovered. None of the infants had evidence of an abnormal bleeding tendency or reduction of blood platelets. In general, the only problem of serious nature seemed to be the threat of kernicterus, the incidence of which might have been even higher save for the use of exchange transfusion, which was applied as our experience with this group began to develop.

Blood Groups and Serology.—The blood groups of the infants and their mothers are shown in Table 1. The incidence of Rh-negative mothers was high, especially if the fact was considered that the group contained about 25% Negroes. However, 4 of the 11 Rh-(D) negative women among the 33 mothers had Rh-negative infants. Moreover, four of the Rh-negative mothers whose infants were Rh positive were uniparae, a fact which in the absence of transfusions in itself speaks against Rh isoimmunization. In any event, Rh immunization was carefully excluded in all cases by multiple tests with Group O cells. The frequency of Rh-negative mothers seemed partly explained by the fact that their Rh type was usually known to the attending obstetricians, and the infants accordingly received closer attention with respect to jaundice than did those born of Rh-positive mothers.

If it is remembered that the 38 cases of Group I A were selected solely on the basis of the clinical symptom of jaundice, which was not otherwise accounted for, the fact that each of the infants proved to be incompatible with the mother in the ABO system becomes very striking indeed. The proportion of A to B infants was 29 to 9, or slightly more than 3 to 1, not unlike the proportion of A to B in the general population of the area.[4] All of the pregnancies proved to be of the type mother O, infant A or B. No examples of mixed heterospecific pregnancy of the type mother A, infant B or vice versa were encountered. A further point of interest was the subgroup of the infants of Blood Group A. As shown by Witebsky and Engasser [5] and confirmed in our earlier studies,[1] the development of A_1 characteristics is often incomplete in the newborn period. Retesting is therefore necessary in all infants giving the reactions of A_2 in the newborn period. Among the 29 A infants, 13 gave A_1 reactions at birth. Of the remainder, three were not tested with

TABLE 1.—*Essential Data on Group I*

Case No.	Blood Groups * Mother	Blood Groups * Infant	Pregnancy No.	Icterus Onset, Hr.	Bilirubin Max., Mg./100 Cc.†	Hemoglobin Minim., Gm./100 Cc.‡	Retic., %†	Nucleated RBC	Spherocytosis	Liver	Spleen	Maternal Serology ‡ Titers Saline	Gum Acacia	Witebsky §	Hemolysin Test	Infant Serology Direct Coombs's Test	Indirect Coombs's Test	Saline Agglutination	Outcome
										Group I A									
1	O neg.	A_{2-1} pos.	4	2	8.3 (1)	9.0	10	+	+	+	−	256	1,024	1,024	++	−	1:8	1:2	Simple transfusion; recovered
2	O neg.	A_{2-1} pos.	1	2	19.0 (1)	12.0	25	−	+	±	−	128	4,096	512	Tr.	−	1:32	1:2	Exchanged; recovered
3	O pos.	A_1 pos.	3	12	29.0 (4)	11.5	32	+	+	+	−	256	4,096	256	+	−	1:8	1:1	Exchanged; recovered
4	O pos.	A_{2-1} pos.	3	10	31.0 (3)	9.8	24	+	+	−	−	2,048	16,000	1,024	++	−	1:32	−	Kernicterus; survived
5	O neg.	A_{2-1} pos.	3	16	9.3 (2)	10.3	13	−	+	±	−	512	2,048	256	++	−	1:4	1:1	Transfusion; recovered
6	O pos.	A_1 pos.	2	<24	18.8 (3)	17.3	6	−	+	±	−	256	4,096	8	+++	−	1:4	1:1	No treatment; recovered
7	O pos.	A_1 pos.	1	<24	27.9 (3)	11.0	30	+	+	+	−	1,024	8,192	16	++	+	1:1	−	Transfusion; recovered
8	O pos.	A pos.	1	10	"Deep icterus"	18.0	?	?	?	?	?	256	2,048	128	Tr.	?	?	?	Kernicterus; died
9		A_1 pos.	2	8	22.0 (3)	20.0	?	−	−	+	−	128	1,024	256	?	+	1:4	−	2 exchange transfusions; recovered
10		A_{2-1} pos.	3	1	14.9 (3)	13.7	26	+	+	+	±	64	2,048	2	++	−	1:4	−	Exchanged; recovered
11	O rh'	A_2-? pos.	1	12	11.0 (4)	12.3	6	+	+	+	−	512	4,096	1,024	++	−	1:8	1:2	Recovered
12	O neg.	A_2-? pos.	1	10	8.3 (2)	8.5	23.6	+	+	+	+++	256	2,048	64	Tr.	Neg.	1:8	−	Transfused; died
13	O pos.	A_1 pos.	6	12	11.3 (1)	11.5	30	−	+	±	+++	64	256	2	?	+	1:2	−	Transfused; recovered
14	O pos.	A pos.	2	Birth	6.8 (3)	12.0	15	−	+	±	+	128	?	32	?	?	?	?	Transfused; recovered
15	O pos.	A pos.	2	12	20.0 (4)	10.5	?	−	±	±	+	512	4,096	128	+	+	1:2	1:1	† kernicterus; lived
16	O neg.	A_{2-1} neg.	2	<24	?	15 (8)	?	−	−	−	−	256	1,024	64	?	−	1:1	Neg.	No treatment; normal
17	O neg.	A_1 pos.	1	<24	14.3 (2)	9.3 (5)	..	−	+	+	−	256	4,096	16	+	−	1:4	1:1	No treatment
18	O pos.	A_{2-1} pos.	3	<24	27.0 (1)	15.7	?	−	?	−	−	128	2,048	64	+	Neg.	1:4	1:1	No treatment; recovered
19	O pos.	A_2 pos.	1	12	13.8 (1)	9.5 (4)	..	+	+	+	−	256	8,192	256	..	−	1:16	1:2	No treatment; recovered
20	O neg.	A_2-? neg.	4	24	6.8 (2)	10.5	3.8	−	+	±	−	128	1,024	64	++	−	1:4	−	Transfused; recovered
21		A_1 pos.	2	24	9.6 (5)	11.7	3.7	−	?	±	−	512	2,048	?	?	?	?	?	No treatment; recovered
22	O neg.	A_1 pos.	3	10	13.0 (1)	12.2	?	−	?	−	−	512	2,048	?	?	?	?	?	2 transfusions; recovered
23		A_1 neg.	4	Birth	9.9 (10)	8.2	4.0 (14)	−	?	±	±	256	1,024	256	?	−	1:1	−	1 transfusion; recovered

24	O pos.	A1	pos.	3	<24	?	?	?	+	?	+	+	256	2,048	?	?	—	?	—	Transfused; recovered
25		A1	pos.	5	Birth	17.0 (1)	9.6	20	+	+	±	—	256	8,192	512	++	+	1:16	1:1	Exchanged; recovered
26	O neg.	A2-1	neg.	5	Birth	Icteric at 12 days	8.5	4.6 (12)	—	+	+	—	512	8,192	128	++	—	1:2	1:1	Transfused; recovered
27	O pos.	A2-1	pos.	2	6	Mild at 1 day	15.8	?	?	?	+	+	64	512	2	—	—	?	?	No treatment; recovered
28	O pos.	A1	pos.	2	<24	8.1 (1)	10.7	30	—	±	+	—	128	512	...	—	—	—	—	Transfused; recovered
29	O neg.	A1	pos.	5	24	13 (2)	11.5	6 (6)	—	—	±	—	128	256	8	—	—	—	—	Transfused; recovered
30	O pos.	B	pos.	2	< 9	27 (4)	15.1	30	—	+	+	±	128	512	64	++	+	1:1	—	Recovered; later athetosis
31	O pos.	B	pos.	1	17	11.8 (1)	8.5	23	+	+	+	—	128	512	256	+	—	1:2	1:1	2 transfusions; recovered
32	O pos.	B	pos.	4	<24	.....	....	7.6	—	+	±	—	256	4,096	256	++	—	1:8	1:1	No treatment; recovered
33	O pos.	B	pos.	2	Birth	?	11.3	?	—	?	—	—	256	2,048	32	?	—	1:1	—	No treatment; recovered
34	O pos.	B	pos.	3	<24	29.5	12.6	30	—	+	+	++	256	4,096	1,024	Tr.	—	1:16	1:1	Exchanged; inspissated-bile syndrome
35	O pos.	B	pos.	3	Birth	28.9 (3)	8.5	?	?	+	+	+	128	1,024	64	++	—	1:1	—	Kernicterus; died
36	O pos.	B	pos.	2	<12	31.5 (3)	11.3	25	+	+	±	±	256	1,024	64	Hard to neutralize ?	—	?	—	Recovered; 4 mo. later still hepatosplenomegaly
37	O pos.	B	pos.	3	<24	16.1 (1)	9.0	12	—	+	+	—	64	256	2	?	—	?	—	Transfused; recovered
38	O pos.	B	pos.	3	<36	26.1 (4)	13.0	10	—	+	±	—	128	512	8	—	—	—	—	No treatment; recovered
										Group I B									
39	O pos.	A1	pos.	2	3 days	22.4 (5)	11.3	?	—	+	+	+	512	8,192	256	....	—	1:8	1:1	No treatment; recovered
40	O pos.	A2-?	pos.	3	<6 days	"Deep icterus"	13.0	0.2 (7)	—	?	±	—	32	256	512	?	—	?	1:1	Kernicterus; survived
41	O pos.	A2-?	pos.	8	3 days	13.2 (8)	15.0	?	—	?	+	—	1,024	8,192	256	?	—	1:8	1:1	No treatment; recovered
42	O pos.	A1	neg.	3	3 days	25.0 (5)	8.0	22	—	±	+	—	64	1,024	8	?	—	1:1	—	Inspissated-bile syndrome; recovered; later athetosis
43	O pos.	A1	pos.	3	3 days	54 (8)	13.2	3.0	+	?	+	±	128	512	2	?	—	—	—	Inspissated-bile syndrome; ? kernicterus; survived
44	A neg.	A1	neg.	?	<3 days	9.6 (28)	15.0	?	?	?	±	—	...	.....	...	—	—	—	—	Inspissated-bile syndrome; recovered

* Where the subgroup of the A infants is not specified, it was not determined. A_1 indicates infants giving A_1 reactions; A_2-?, no retesting of an infant giving A_2 reaction at birth; A_{2-1}, original reaction on retesting changed to A_1.

† Figures in parentheses indicate the day of life of the infant on which these particular values were obtained.

‡ Titer values refer to reciprocals of the dilution.

§ Titer in AB serum after partial neutralization of saline agglutinins.

respect to their subgroup, and four others who were typed as A_2 initially could not be retested at a later date. The nine infants originally typed as A_2 who could be retested all proved later to belong to subgroup A_1. The absence of infants with proved permanent A_2 characteristics contrasted with an incidence of 20% of permanent A_2 infants in a random control series.[1]

The secretor status of the infants was ascertained in 28 instances. Three of the patients, or slightly more than 10%, proved to be nonsecretors for A or B. The saliva of one of these infants (Case 13) was retested several times up to one year after birth, always with clearcut negative results. In another case the test was repeated at 2 months of age with the same negative results (Case 26).

The maternal anti-A or -B isoantibody patterns in the large majority of cases showed deviations from those described for the obstetrical group. Chart 1 shows

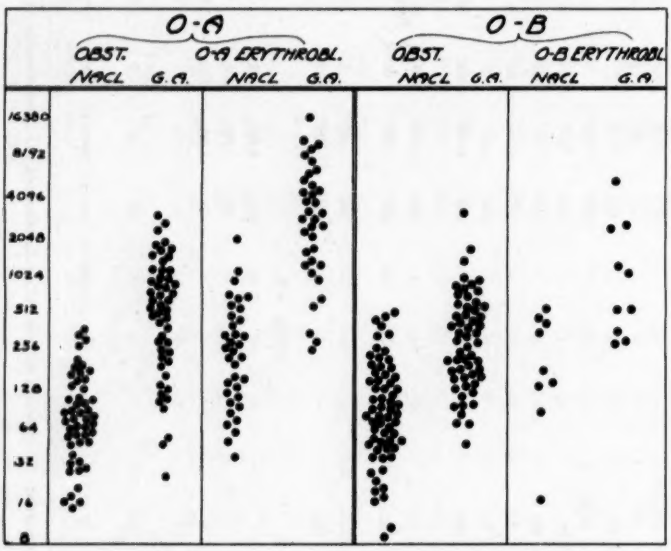

Chart 1.—α and β titers in saline and gum acacia.

the α and β titers in saline and gum acacia media. Considerable overlapping with the obstetrical control group is evident, but the range of titers is distinctly higher, especially in the acacia medium. The highest anti-A titer observed was 2,048 in saline and 16,000 in gum acacia in Case 4. The spread between saline and acacia titer shown by the individual serum was generally greater than in the control group and extended over five tubes in several cases (Chart 2).

The demonstration of "immune" antibody specific for the infant's blood group after partial neutralization of α and β agglutinins by soluble A and B substance was successful (Witebsky's test) in 22 of 35 cases tested (Table 1). In two additional instances the saline agglutinins could not be neutralized unless greatly diluted, a type of reaction shown in earlier studies to occur under similar conditions as the typical Witebsky reaction [1] and believed to have the same significance. In 11 cases the reaction was equivocal or frankly negative. Titration of neutralized sera by means of the indirect Coombs test gave results which were almost exactly parallel to those obtained with the AB-serum technique and were therefore not tabulated.

Twenty-two of 26 maternal sera in the O-A group contained hemolysins effective against adult A_1 cells. Since hemolysins of such activity had been found in a significant number of control cases,[1] 18 sera were tested simultaneously against the infants' or fresh normal cord blood, following a suggestion by Mollison.‡ As shown in Table 2, adult A_1 cells were usually but not always hemolyzed to a greater extent than A_2 cells, which in turn were often paralleled by cord A_1 cells or the cells of the affected A infants. Normal cord A_2 cells were not hemolyzed to any extent by any of the maternal sera. Thirteen of eighteen O-A combinations tested showed hemolysis of newborn erythrocytes by the maternal serum.

The serologic studies on the infants were nearly always made on venous blood and capillary blood, cord blood being rarely available. From serial observations, it was concluded that this factor did not significantly affect the results. A positive

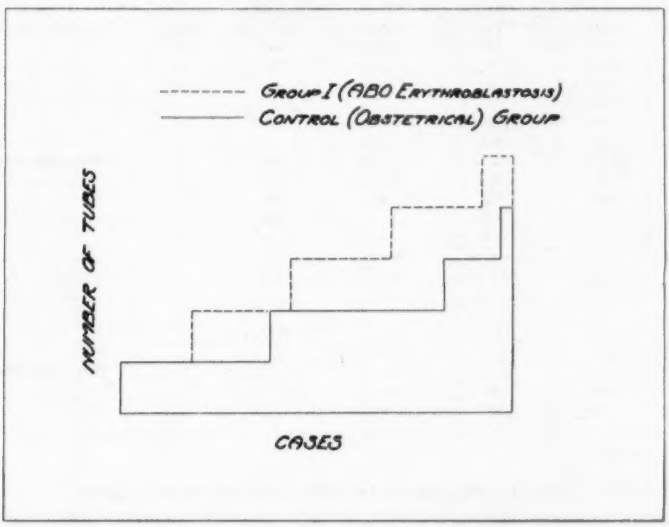

Chart 2.—Comparison of the spread between saline and acacia titers shown by individual serum with that of the control group.

direct antiglobulin test was obtained in 6 of the 37 infants. The reaction was always weak, though definite. The antiglobulin serum used was one which had proved highly satisfactory in the detection of Rh immunization.

An attempt was made in 23 cases to elute antibody of α and β specificity from the erythrocytes of the infants by a method previously described[1] and almost invariably successful in demonstrating Rh antibody coating the fetal red cells in Rh hemolytic disease.§ In the present study the attempt was successful only in three instances, in each of which the direct Coombs test had been positive (Cases 4, 9, and 15).

Free isoantibody in the plasma specific for the infant's own blood group was demonstrable either as a saline agglutinin or by means of the indirect Coombs test

‡ Mollison, P.: Personal communication to the authors.

§ Zuelzer, W. W., and Kaplan, E.: Unpublished data.

with adult erythrocytes in 26 of 29 cases tested. Interestingly, in the case of A infants, the *a* antibody found usually proved to have a_1 specificity. A typical protocol illustrates the failure of the antibody to react with A_2 cells (Table 3).

TABLE 2.—*Hemolysins in Maternal Sera*

Case No.	Test Cells A1	Test Cells A2	Test Cells B	Infant's or Cord A1 Cells	Cord A2	Infant's B Cells
1	+++	.....	++	++	..	.....
2	+++	+	—	Tr.	..	.....
3	++	+	+	+	..	.....
4	+++	+++	+++	++	Tr.	.....
5	+++	+++	Tr.	.....	..	.....
6	+++	+++	.....	+++	+	.....
7	+++	++	.....	++	+	.....
8	++	+	+	Tr.	..	.....
9	++	Tr.	Tr.	.....	..	.....
10	+++	Tr.	.....	++	..	.....
11	++	++	++	+	..	.....
12	+++	+	.....	Tr.	..	.....
13	++	+	—	.....	..	.....
14	+++	.....	.....	.....	..	.....
15	+++	+++	.....	+	..	.....
16	+++	++	—	.....	..	.....
17	+++	.....	.....	+	..	Hemolysis present
18	+	+	Tr.	+	..	.....
19	++	Tr.	+	Tr.	..	.....
20	++	++	.....	++	..	.....
23	+++	++	+	.....	..	.....
25	+++	+++	+++	+	..	.....
26	+++	+++	+++	++	..	.....
27	+	.....	—	.....	..	.....
28	+	.....	—	—	—	.....
29	+	Tr.	.....	Tr.	—	.....
31	Tr.	—	++	.....	..	.....
32	.....	.....	.....	.....	..	Hemolysis present
33	+++	+	++	.....	..	.....
34	++	Tr.	+	.....	..	Tr.

TABLE 3.—*Protocol of Antibody Studies in Infant's Blood*

	Case 9																
	Test Cells																
	A1					A2				B				O			
	1:1	1:2	1:4	1:8	1:16	1:1	1:2	1:4	1:8	1:1	1:2	1:4	1:8	1:1	1:2	1:4	1:8
Infant's serum																	
Titered in saline.....	—	—	—	—	..	—	—	—	—	+	—	—	—	—	—	—	—
Titered in AB serum.....	+	+	±	—	..	—	—	—	—	+	±	—	—	—	—	—	—
Indirect Coombs's test....	+	..	..	..	..	—	..	..	..	..	..	..	..	—	..	..	..
Eluate from infant's cells	+	+	±	±	—	—	—	—	—	..	..	..	..	—	—	—	—

As shown in Table 4, the adequately studied maternal sera invariably exhibited some abnormality in the antibody pattern whenever homologous antibody was found in the infants' blood. Conversely, whenever adequate testing was possible, the infants of mothers with abnormal antibodies antagonistic to the fetal blood group had free antibody of the same specificity in their own plasma. The various techniques used for the demonstration of maternal immune isoantibody generally gave parallel results, but occasionally one or the other test was negative when the remainder were positive. Thus, in a few instances the hemolysin test failed while

the Witebsky test was positive and free antibody was present in the infants' serum. No one test alone gave perfect correlations with the clinical picture, but a combination of several of the tests usually gave positive results. The vagaries sometimes encountered are well illustrated by the following case.

CASE 10.—Mrs. P. had previously been delivered of two infants of blood Group A_1, both of whom had been icteric. The first child (Case 8) had died with kernicterus. Serum obtained after the birth of each of these children had given a strongly positive Witebsky reaction. The third infant was again Blood Group A_1, secretor, became icteric within one hour after birth, and had marked reticulocytosis and spherocytosis of the blood. At this time the maternal serum gave a negative Witebsky reaction, although the hemolysin test was strongly positive, the acacia

TABLE 4.—*Maternal Antibody Patterns in O-A*

Case No.	Elevated Saline Titer	Absolutely or Relatively Elevated Gum Acacia Titer	Witebsky Reaction	Hemolysins Against Fetal Cells	Free Antibody in Infant's Plasma	
1	−	−	+	+	+	
2	−	+	+	−	+	
3	−	+	+	+	+	
4	+	+	+	+	+	
5	−	−	+	−	+	
6	−	+	−	+	+	
7	+	+	−	+	+	
8	−	±	+	−	+	
9	−	±	−	?	+	Siblings
10	−	+	−	+	+	
11	+	+	+	+	+	
12	−	+	+	Tr.	+	
13	−	−	−	?	+	
14	−	?	±	?	+	
15	−	+	+	+	+	
16	−	−	+	?	+	
17	−	+	−	+	+	
18	−	+	+	+	+	
19	−	+	+	−	+	
20	−	+	+	+	+	
21	−	−	?	?	?	Siblings
22	−	−	?	?	?	
23	−	−	+	?	+	
24	−	−	?	?	?	Siblings
25	−	+	+	+	+	
26	−	+	+	+	+	
27	−	−	−	−	?	
28	−	−	−	−	−	
29	−	−	−	−	−	

anti-A titer was five tubes higher than the saline titer, and the infant's plasma contained free α antibody. Three weeks post partum the maternal serum again gave a negative Witebsky reaction. Concomitantly tested stored serum obtained during the second confinement gave a titer in AB serum of 1:256 after neutralization with AB substance

Serologic Failures.—In four adequately tested cases (Cases 27 to 29 and 38), none of the serologic tests performed on mother and child gave positive results. In each case, the clinical picture was that of mild disease, yet the objective findings were not distinguishable from those of the group as a whole. Thus, three of the four infants had definite anemia, three exhibited spherocytosis, and one had a reticulocytosis of 30%. The bilirubin level of one infant was 26.1 mg. per 100 cc. on the fourth day of life. The sibling of one child (Case 27) had been icteric on the first day of life, supporting the assumption that maternal immunity played a part in the patient's condition. In another case to be described later (Case 28),

the survival of transfused A erythrocytes was shorter than that of simultaneously administered O cells, further substantiating the specific character of the hemolytic process in this infant.

Erythrocyte Survival Studies.—The survival of transfused erythrocytes by the "double exchange" method was studied in three cases. In each case Group O cells and cells of the same type as the infant were transfused in approximately equal amounts under the conditions and precautions detailed in the previous paper.[8] In addition, a transfusion of labeled Blood Group A erythrocytes only was given in Case 10. Charts 3 and 4 show the significantly shortened survival of the homologous cell type of adult erythrocytes in all cases, with significantly greater survival of the O cells in the three cases in which they were given. Case 7 was of particular interest in that two successive studies of the differential survival of Group A and Group O

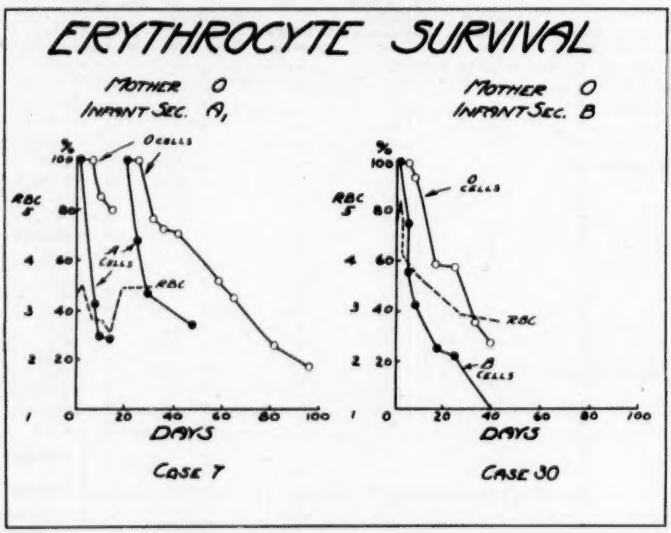

Chart 3.

cells were made. This infant was the product of the mother's first pregnancy, admitted at 3 days of age with a history of jaundice within 24 hours and showing at this time a definite anemia, marked hyperbilirubinemia, reticulocytosis of 30%, and spherocytosis. The serologic findings (Table 1) were indicative of maternal isoimmunization against A, as shown by a high saline titer and gum acacia titer, hemolysis of cord A_1 erythrocytes by the maternal serum, and the positive direct as well as the indirect Coombs test of the infant's blood. Transfusions of low-titered O M blood and A_1 N blood were given on the sixth day of life (Table 5). While the survival of the O cells followed the expected pattern, the count of A cells fell rapidly, the slope of the curve indicating complete destruction in about 30 days. On the 21st and 22d days of life, a second set of O- and A-cell transfusions was given, the counts obtained on the following morning being regarded as the base line. Although by this time there was no longer free antibody present in the infant's plasma and the jaundice had subsided, the A cells were still being eliminated far more rapidly than the O cells, though somewhat more slowly than in the beginning.

The duplication of the original curves by those obtained in the second experiment establishes once more the validity of the method. In addition, the rapid elimination of homologous cells at the end of the first month indicates that the hemolytic process may continue for a greater length of time than the clinical data would lead one to believe. It is also in keeping with the results of experiments on the apparently normal infants described in the previous paper [3] in whom homologous cells were rapidly eliminated even in the absence of a demonstrable abnormality in the serologic pattern. The findings confirm again that the physiologic method of study, namely, the survival of labeled erythrocytes, is a more sensitive index of the hemolytic activity than the presently available serologic methods.

In Case 30, that of a Group B infant of an O mother, the elimination of the B cells was appreciably shorter than that of the O cells transfused a day earlier. In

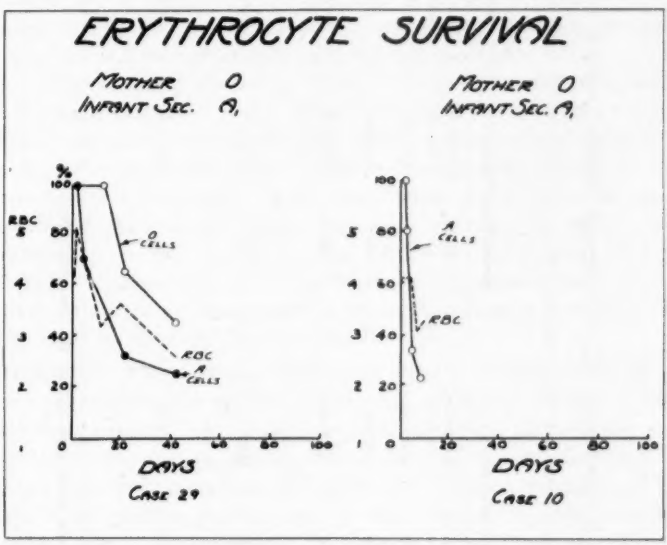

Chart 4.

this patient, both the maternal and the fetal serologic findings had indicated a significant state of maternal sensitization. The clinical picture was that of ABO hemolytic disease, and the rapid elimination of Group B cells was expected.

In the third case, Case 29, neither the clinical nor the serologic findings were as clear-cut. The child was originally regarded as a normal infant, admitted on the second day of life with a hemoglobin value of 15 gm. but a history of jaundice within the first 24 hours. The main reason for admission lay in the fact that the mother was known to be Rh negative. Although the infant proved to be Rh positive, Rh isoimmunization could be excluded. The bilirubin level on admission was 13 mg., but fell rapidly to 2.6 mg., and the child throughout his short hospital stay was active and vigorous. Although there was an incompatibility, mother Group O, baby A_1 secretor, the maternal antibody studies revealed nothing out of the ordinary (Table 1), and no free antibody against A could be demonstrated in the infant's serum. Chart 3 shows, however, that the homologous cells transfused were elim-

TABLE 5.—*Data in Four Cases in Which Erythrocyte Survival Studies Were Made**

Case	Mother	Infant Recipient	First Transfusion			Second Transfusion			Inagglutinated Cells			
									Pretransfusion		Post-Transfusion	
			Day	Amount, Cc.	Type Donor Blood	Day	Amount, Cc.	Type Donor Blood	Anti-A or B Serum	Anti-M Serum	Anti-A or B Serum	Anti-M Serum
7	OM CDe	A_1MN cde Secretor BW, 7 lb. 4 oz. (3,290 gm.)	6	40	OMN cde	6	40	AN cde	19,000	2,000	287,000	525,000
			21	30	OM cde	22	35	A_1N cde	.....	.....	680,000	590,000
30	OMN cde	BM cDE Secretor BW, 8 lb. 9 oz. (3,880 gm.)	6	30	OMN cDE	7	30	BN cDE	52,000	5,000	240,000	320,000
29	OMN cde	A_1MN cDE Secretor BW, 8 lb. 13 oz. (4,000 gm.)	7	40	OMN D	8	40	A_1N D	31,000	4,000	302,000	299,000
10	OM CDe	AM cde Secretor BW, 8 lb. 12 oz. (3,980 gm.)	3	30	A_1N cde	..	..	.....	.....	1,000	.....	209,000

* Infants studied because of jaundice attributable to causes other than ABO or Rh incompatibility.

inated more rapidly than O cells, although more slowly than in the other three cases in which Ashby studies were made. This case would seem to represent a link between the completely asymptomatic cases described in a previous paper and the more severe manifestations shown by Cases 7, 10, 29, and 30. The slope of the curve of elimination of the homologous cells fits this interpretation, being steeper than in the cases of "normal infants" but more gradual than in the other cases of ABO hemolytic disease studied by the Ashby method.

In the last case, only A cells could be given, for technical reasons, but their elimination was so rapid as to leave no doubt about the fact that they were being destroyed with abnormal rapidity. The findings confirm the group-specific hemolytic mechanisms in ABO hemolytic disease, based hitherto only on the isolated findings of the British authors.[10]

Correlations.—The clinical picture observed in the 38 infants of Group I A was remarkably uniform and corresponded well to the condition designated as icterus precox by Halbrecht [6] or to a mild form of hemolytic disease of the newborn, there being no sharp distinction between the two. In agreement with other authors,|| the features typical of the group were found to be a mild or moderate hemolytic anemia, usually characterized by spherocytosis, and a variable degree of bilirubinemia. As in physiologic jaundice and in Rh hemolytic disease, the intensity of the icterus seemed to correlate better with individual variations of some other factor, presumably hepatic in nature, than with the severity of the hemolytic process. Variations in the intensity of the icterus in combination with another individual factor also seemed to be significant in determining the occurrence of kernicterus and thus the eventual outcome, since brain damage seemed to be virtually the only serious threat to these infants.

The striking fact that in a group of the cases selected on the basis of unexplained early icterus the combination mother O, infant A or B was present in each case has already been stressed. The correlation between clinical pictures and abnormal antibody patterns was not so perfect. About 10% of the 36 adequately studied cases failed to show deviations from the ordinary patterns of maternal and infantile sera. While it was possible that in some or all of the serologically negative cases the symptoms were due to some other unrecognized mechanisms and that O-A or O-B incompatibility was purely accidental, the available evidence did not favor such an assumption, especially in the case with the affected sibling and in the case showing differential elimination of A cells. It would not seem permissible to exclude the four cases in question merely because the laboratory tests available at this time failed to give the expected results. Rather, they should be considered as probable serologic failures requiring further improvement in techniques. In the present context, however, the positive findings must be considered as more significant than the failures because of the contrast which the group as a whole forms to the obstetrical control group. The correlation of antibody patterns and clinical pictures of about 90% then appears surprisingly good. It represents, after all, an attempt to correlate two rather ill-defined phenomena: on the one hand, a clinical symptom-complex which merges without sharp borders into physiologic variants, and on the other, a group of tests attempting to distinguish between antibodies somewhat arbitrarily designated as "natural" and antibodies of the same specificity

|| References 7-10.

but possessing special immune characteristics. The fact that no one single test approached the correlation shown by the Coombs test in Rh immunization does not detract from the significance of the findings obtained with a battery of procedures. From a practical viewpoint, however, the serologic methods used here for the demonstration of pathologic ABO incompatibility obviously still leave something to be desired. As a screening test, the indirect Coombs test of the infant's plasma against homologous adult erythrocytes seemed to be the most useful procedure. Of the tests applicable in the prenatal diagnosis, the hemolysin test would seem to offer the best screening procedure to laboratories having cord blood available.

Group I B (Delayed Icterus).

The high degree of correlation with serologic patterns and the consistent clinical picture of the group just described would seem to justify the use of that group as a basis for comparison with the other categories of patients. The general validity of the serologic and hematologic diagnosis seemed well supported by our observations. Applying these criteria to the second group (I B), distinguished from the earlier cases only in that icterus was not actually observed until after the first day, it became apparent that several cases were indeed additional examples of ABO incompatibility. Since the infants were referred to us from various nurseries in the city with different standards of observation, it is possible, and indeed likely, that icterus had been present earlier but went unnoticed until it became intense. This was almost certainly true in Case 40, that of an infant admitted with deep jaundice and signs of kernicterus at 7 days of age and alleged to have become icteric only in the last 24 hours.

The first four cases of this group (Cases 39 to 42), listed in Table 1, fulfilled the diagnostic criteria of ABO hemolytic disease. The saline and gum acacia titers of the maternal sera are included with those of Group I A in Chart 1. In each case, antibody antagonistic to the infant's blood group was found in the plasma of the patient; in three cases, the maternal Witebsky reaction was strongly positive, two of the mothers had had previous icteric children, the blood of two of the babies showed spherocytosis, and one showed marked reticulocytosis. The other three infants were admitted so late that this last feature was not to be expected.

In Case 43, the infant was admitted deeply icteric and with a grossly infected umbilicus at the age of one week. The blood culture was sterile, however, and in the absence of serologic evidence favoring ABO incompatibility a satisfactory diagnosis was not reached. The last case in the group was likewise unexplained, but could be eliminated since both mother and infant were A Rh negative.

The addition of four cases from the group of deeply icteric infants whose jaundice was delayed or of unknown onset raises to 42 the number of cases attributable to ABO incompatibility thus far and adds one case each to the number of cases of kernicterus and of the inspissated bile syndrome. The correlations between clinical picture, blood group combinations, and serologic findings were only slightly less satisfactory than in the group with early icterus.

Group II

It is of interest to compare the 44 cases of Group I with the cases of Group II in which jaundice was also the chief symptom but was accounted for on other grounds. As shown in Table 6, 5 of the 10 infants were compatible with their

TABLE 6.—*Data on Group II*

Case No.	Blood Groups: Mother	Blood Groups: Infant	Pregnancy No.	Icterus Onset	Bilirubin Max.*	Hemoglobin Minim.	Symptoms	Findings	Unusual Antibody: Mother	Unusual Antibody: Infant	Diagnosis
45	O pos.	B pos.	1	4 days	?	?	Deepening icterus, prematurity, spasticity, convulsions	Purulent meningitis	—	—	Bacterium coli meningitis
46	O pos.	A_{2-1} pos.	2	3 days	15.3 (4)	22	High fever; good response to antibiotics	Positive blood culture	—	—	Staphylococcus sepsis
47	O pos.	O pos.	2	2 days	5 (9)	?	Diarrhea, prematurity, icterus	.....	—	—	Inspissated bile syndrome ? cause, diarrhea
48	A pos.	A pos.	4	<12 hr.	?	15.4	Convulsions, petechiae, abdominal mass, vomiting	Oliguria	—	—	Renal vein thrombosis
49	O pos.	O pos.	1	? prolonged	10 (8)	15.0	Vomiting, dehydration	Diaphragmatic hernia	—	—	Diaphragmatic hernia
50	A pos.	A pos.	1	Birth	9.2	7	Hepatomegaly, splenomegaly	Abnormal liver function tests	—	—	Cirrhosis, proved by autopsy
51	O pos.	A pos.	2	Birth	30	17.3	Hepatomegaly, icterus, splenomegaly	Abnormal liver function tests, cold agglutinins	—	—	Hepatitis
52	O pos.	B pos.	1	Birth	4.2	10.1	Icterus, slight hepatosplenomegaly	Positive urine culture, abnormal liver function tests	—	+ Hemolysin	Hepatitis, ? pyuria
53	O pos.	A_1 pos.	1	12 hr.	19.8	11.5	Fever, dehydration, distention	Abnormal liver function tests	—	—	Hepatitis
54	A neg.	O pos.	1	<48 hr.	30	?	Persistent icterus; mother splenectomized	Spherocytosis, increased fragility	—	—	Congenital hemolytic icterus

* Figures in parentheses indicate the day of life of the infant on which these particular values were obtained.

TABLE 7.—*Data on Group III*

Case No.	Blood Groups: Mother	Blood Groups: Infant	Reason for Study	Pregnancy No.	Maternal Serology: Saline	Maternal Serology: Gum Acacia	Maternal Serology: Witebsky	Infant	Remarks
55	O neg.	O pos.	"High" saline anti-A titer	?	Anti-A 512 Anti-B 32	Anti-A 1,024 Anti-B 64	Neg.	Normal	Postpartum anti-B rises to saline 1:128, gum acacia 1:1,024
56	O neg.	O pos.	Rh-negative mother	1	.....	.....	....	Normal	Rh ruled out
57	O neg.	A neg.	"High anti-A titer"	1	Anti-A 128 Anti-B 32	Anti-A 512 Anti-B 64	Neg.	Normal	No unusual antibodies found
58	O rh'	B pos.	Rh-negative mother	3	Anti-A 32 Anti-B 128	Anti-A 128 Anti-B 256	.... Neg.	Normal	No unusual antibodies found
59	O neg.	A_{2-1} neg.	Rh-negative mother, high anti-A	1	Anti-A 512 Anti-B 64	Anti-A 1,024 Anti-B 128	64	Reticulocytosis, anemia, positive indirect Coombs's test	Mild O-A hemolytic disease; no treatment
60	O neg.	A_1 pos.	Previous case with maternal antibodies	2	Anti-A 512	Anti-A 4,096	512	Icteric in 24 hr., HGB. 9.9, liver enlarged, positive indirect Coombs's test	Mild O-A hemolytic disease; no treatment
61	O neg.	A_1 pos.	Rh-negative mother	2	Anti-A 256 Anti-B 512	Anti-A 8,192 Anti-B 1,024	256	Mild anemia, positive indirect Coombs's test	Mild O-A hemolytic disease

mother in the ABO system, and in none of the remaining 5 cases did the maternal or infantile serologic patterns indicate significant isoimmunization against A or B. The correlation in this group was zero, making the findings in Group I even more significant.

Group III

Group III was studied solely because the mothers were known to be Rh negative or because in the course of examining the sera of these women for possible antibodies, unusual anti-A or -B antibodies had been reported. Four of the seven infants proved normal in every respect (Table 7, Cases 55 to 58). Two of these were of Blood Group O, and in the other two, though they were incompatible with their mothers, no abnormal antibodies α or β could be found. The last three patients (Cases 59 to 61) were of interest because they permitted a reversed test of correlations, beginning with the serologic evidence and showing the validity of a diagnosis based on atypical isoantibodies in the ABO system.

Case 59.—Mrs. G. was referred for Rh studies during her second pregnancy. Her first child had died at the age of 6 months with hydrocephalus but had not been icteric at birth. She proved to be Blood Group O, Rh negative, but had no Rh antibodies in her serum one month prior to delivery. The anti-A titer in saline was 512, in gum acacia, 2,048. Other tests were not done at this time, but the obstetrician was instructed to observe the newborn infant closely. At term the maternal anti-A titers were unchanged, but the serum gave a strongly positive Witebsky reaction and was moderately hemolytic. The infant was Blood Group A_1, secretor, giving A_2 reactions at birth but A_1 reactions at a later date. Although he did not become jaundiced until the third day, the hemoglobin level of the cord blood was 13.0 gm. per 100 cc., and that of the capillary blood fell to 11.1 gm. within one week. The reticulocyte counts during this time ranged from 8 to 10%. The cord serum agglutinated A_1 cells both in saline and in AB serum. Yet clinically this infant was regarded as normal by the attending physicians.

Case 60.—Mrs. G. obligingly became pregnant again within the year. Again the infant was Blood Group A_1, secretor, and again Rh sensitization was thoroughly excluded. At the time of delivery the maternal saline and gum acacia titers were unchanged, the Witebsky reaction was again positive, and hemolysis of adult and cord A_1 cells was marked. The serum of the second infant also agglutinated A_1 erythrocytes in saline and gave an indirect Coombs test of 1:8. Although the attending physician again regarded this infant as normal, the cord bilirubin was 3.1 mg. per 100 cc., and the baby was icteric on the first day of life and at 10 days was pale and had a hemoglobin concentration of 9.9 gm. per 100 cc.

Though the condition of neither child required treatment, and both would have escaped attention, it is clear that both infants showed effects of ABO incompatibility. These cases and Case 61, which was similar in every respect, show the usefulness of the serologic procedures in tentative prenatal diagnosis of ABO hemolytic disease.

Group IV

The last group of patients was studied for miscellaneous clinical reasons, chiefly anemia in the newborn period. Usually the nature of the anemia became clear before the serologic tests were even completed, but in several instances the etiology remained obscure. Table 8 shows that six infants (Cases 63 to 68) had suffered major hemorrhages. In four cases the anemia was not explained. In one of these both mother and infant were Blood Group O. In the three others no abnormality in antibody patterns could be found, and the clinical features did not suggest ABO hemolytic disease as seen in Group I. In the last two cases (Cases 73 and 74) mother and child were incompatible, and in both instances the isoantibody pattern

TABLE 8.—*Data on Group IV*

Case No.	Blood Groups		Complaint	Pregnancy No.	Symptoms	Maternal Serology			Diagnosis
	Mother	Infant				Saline	Gum Acacia	Witebsky	
62	O pos.	B pos.	Anasarca	1	Mother preeclamptic fetal distress, edema, HGB. 12.0	Anti-A 1,024 Anti-B 1,024	Anti-A 2,048 Anti-B 1,024	128 Neg.	Anasarca, ? cause
63	O pos.	B pos.	Anemia	1	Massive hemorrhage	Not remarkable			Hemorrhagic disease
64	O pos.	B pos.	Anemia	6	Hematemesis, melena	Not remarkable			Hemorrhagic disease
65	O pos.	B pos.	Anemia	1	Vaginal bleeding	Not remarkable			Hemorrhagic disease
66	O pos.	B pos.	Melena	3	Rectal bleeding, slight icterus at 36 hr.	Anti-A 64 Anti-B 64	Anti-A 256 Anti-B 256	... 8	Hemorrhagic disease
67	O pos.	A_1 pos.	Anemia	1	Shock	Not remarkable			Massive hemoperitoneum
68	O pos.	A_1 pos.	Anemia	3	Bleeding from cord	Not remarkable			Blood loss
69	O pos.	O pos.	Late anemia	3	Membranes ruptured early, premature	.....			Prematurity
70	O rh'	A pos.	Anemia	2	Icterus at 48 hr., slowly progressive anemia	Anti-A 256 Anti-B 16	Anti-A 512 Anti-B 64	Neg.	?
71	O neg.	A neg.	Anemia	2	Pneumonia, positive nose culture	Not remarkable			Pneumonia
72	O pos.	B pos.	Anemia	2	Difficult delivery, cyanosis	Not remarkable			? congenital heart disease
73	O neg.	A rh'	Anemia	9	Icteric at 4 days, mother anemic, baby's HGB. 9.9 at 1 wk.	Anti-A 256 Anti-B 128	Anti-A 1,024 Anti-B 512	256 (Hemolysin+)	Mild O-A hemolytic disease
74	O pos.	B pos.	Anemia	6	Moderate icterus at 3 days, bil. 14.0 at 5 days, reticulocytosis; HGB. 9.0	Anti-A 32 Anti-B 256	Anti-A 256 Anti-B 2,048	... 64	Mild O-A hemolytic disease

of the maternal serum was markedly abnormal. Neither infant had been jaundiced on the first day, but in one case (Case 74) the bilirubin level was 14 mg. per 100 cc. at 5 days of age. Both infants recovered.

With the addition of the 3 cases culled from Group III and 2 cases from Group IV, the total number of cases attributable to ABO incompatibility rises to 47 among 74 cases investigated. The results may be tabulated according to the indications for study as shown in Table 9.

COMMENT

The clinical and hematologic observations reported here are in agreement with the findings of Halbrecht,[6] Polayes,[9] Wiener,[8] Grumbach and Gasser,[7] and others who have studied the subject. ABO incompatibility does produce certain pathologic effects in newborn infants, but as a rule only when the maternal isoantibody pattern

TABLE 9.—*Cases Attributable to ABO Incompatibility, with Results According to Indications for Study*

Reason for Study	No. Cases	No. ABO Incompat. Possible	No. Clinically Attrib. to ABO Incompat.	No. Serologically Confirmed
Group I				
Jaundice without other known cause				
A. First 24 hours	38	38	38	33
B. Later	6	5	4	4
Total	44	43	42	37
Group II				
Jaundice, otherwise explained	10	5	—	0
Group III				
Maternal blood group or antibody studies	7	5	3	3
Group IV				
Anemia and miscellaneous conditions	13	12	2	2
Total	74	65	47	42

is abnormal. The nature of the process in the affected infants is clearly a hemolytic anemia, complicated by the relative inefficiency of the newborn liver in dealing with the products of hemoglobin breakdown. The range of clinical manifestations is narrower than that of hemolytic disease due to maternal Rh isoimmunization. In fact, the condition is often so mild that the term "disease" seems too alarming a word to describe it, and Halbrecht's coinage, icterus precox, would seem more apt. Yet the high incidence of neurologic complications, even in cases in which the hemolytic process is unimpressive, shows that the condition is always of potential concern. The distinction between "icterus precox" and ABO hemolytic disease is therefore artificial and misleading. Seen as a whole, the variants form a single disease entity with the shadings in severity and minor variations that one might expect in any etiologically uniform condition. Since most of the cases, fortunately, are quite benign, the practical problem is the appraisal of the individual case, regardless of the label, with respect to severity. Severity, in turn, must be conceived in terms of the intensity of jaundice and the likelihood of kernicterus, which is the chief and virtually only concern in these infants. The practical aspects of management will be dealt with in a later communication. Here it may suffice to state that at present the effort required by the frequency of heterospecific pregnancy, the

laborious character of the tests involved, and the good condition of the infants at birth combine to make routine prenatal studies seem unwarranted. When the infant is born and begins to show clinical evidence of ABO incompatibility, there is ample time to appraise the situation, make the diagnosis, and evaluate and avert the threat of kernicterus. Such a philosophy does imply, however, that the symptom of icterus appearing in the first 24 hours or becoming severe in the next few days requires more attention than may have been paid to it heretofore in many nurseries. On the other hand, icterus should not be regarded as a reason for alarming the parents to the same extent as in Rh isoimmunization if the cause is ABO incompatibility.

The comparison of the infants showing clinical manifestations with those in the obstetrical control group indicates that there is a qualitative as well as a quantitative difference in the maternal antibodies of the two groups. Whether or not the natural α and β agglutinins are the result of immunization with A and B substances, the antibodies demonstrated by the Witebsky technique or the other methods used here evidently possess special immune or hyperimmune characteristics identical with or comparable to those found in persons receiving mismatched blood. The origin of these special antibodies will be dealt with later. It is apparent that the saline agglutinin titers cannot be relied on for diagnosis unless they are well above the range of titers obtained by the same method in normal persons.

The observation that in O-A combinations the offending maternal α antibody has A_1 specificity was first reported by Witebsky [11] and was confirmed by all our pertinent cases. The finding is especially significant in the light of our added observation that all A infants who could be adequately tested were of subgroup A_1 either at birth or on later retesting. The assumption that only A_1 infants are susceptible is supported by our earlier observations that free α antibody may be present in the cord blood of infants of permanent subgroup A_2 without causing recognizable disturbances. A comparative study of Group O cord bloods would be needed to show whether the α antibody passing the placenta normally or always has α_1 specificity.

The question whether the secretor status of the A or B infants plays a part in the pathogenesis of the hemolytic process is not conclusively answered by our findings. There were a few nonsecretors among the affected infants. The number of nonsecretors was somewhat smaller than the incidence expected in a random group, but the discrepancy is not statistically significant in a small series. Grumbach and Gasser [7] reported two nonsecretors in a series of five infants affected by ABO incompatibility whose secretor status they tested. Most other authors found only secretors. No large systematic study of this question has yet been reported. Wiener [8] has expressed the belief that secretor infants are especially liable to harmful effects of heterospecific pregnancy. There is at present no proof that the secretor status influences the effect of maternal immune isoantibodies on the infant.

SUMMARY AND CONCLUSIONS

A comparison of 74 cases of suspected ABO hemolytic disease, designated as the pediatric group, and some 228 cases of unselected heterospecific and homospecific pregnancies, labeled the obstetrical group, showed clear-cut differences. While ABO heterospecific pregnancy ordinarily has no harmful effect on the fetus

or newborn infant, it does have such an effect in certain instances clearly related to the presence of unusual maternal antibodies with special immune characteristics. These characteristics permit a serologic diagnosis in the majority of cases and have been described in detail. The presence of free antibody antagonistic to the infant's blood group in the serum of the newborn correlates with the maternal pattern and is of diagnostic significance.

The condition resulting from the special immunity of the mother against A or B is a hemolytic process of moderate and mild degree accompanied by variable degrees of icterus. The icterus appears to be determined in part by an independent factor, presumably hepatic function. There is no sharp dividing line between so-called icterus precox and ABO hemolytic disease. The only serious threat is the occurrence of kernicterus observed in about 15% of the cases and apparently related to bilirubinemia and to a factor of individual susceptibility.

In O-A hemolytic disease the maternal antibody reaching the fetus was always of A_1 specificity, and all of the affected infants belonged to subgroup A_1, though this point could not always be established at birth. It seems likely that A_2 infants are not susceptible to ABO hemolytic disease. The secretor status of the A or B infants did not seem to influence the effects of the special immune antibodies of the mother.

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EFFECT OF ANTIBIOTICS ON NASOPHARYNGEAL FLORA OF PREMATURE INFANTS

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BEGINNING in 1948, infants admitted to the premature nursery of the Infants' Hospital (Children's Medical Center) were routinely given penicillin and either sulfadiazine or streptomycin in relatively large doses for the first 5 to 10 days following admission. The effect upon mortality appears to have been favorable.[1] During the same period, similar antibiotics and chemotherapeutic agents have been prescribed for certain infants admitted to the premature nursery of the Boston Lying-in Hospital in whom early rupture of membranes, suspected or actual infection in the mother, or abnormal pulmonary ventilation suggested actual or potential infection in the infant. The present study was undertaken to determine the effect of this regimen upon the aerobic flora of the nasopharnynx in the premature infants cared for in these two nurseries.

Cultures from the nose and throat are frequently sterile during the first 24 hours after birth.* Torrey and Reese [8] pointed out that sterility of the upper respiratory tract persists for a longer period in artificially fed premature newborn infants than in breast-fed full-term infants. These same authors reported that the first bacteria to appear in the throat were alpha hemolytic streptococci, anhemolytic streptococci, staphylococci, and Escherichia coli. The incidence of staphylococci increased with age.† Rountree and Barbour [9] found the incidence of pyogenic staphylococci in the nose to be higher in infants of 6 to 7 days of age than in the nurses caring for these infants. They concluded that the mucous membrane of the nose is more suitable for the growth of staphylococci during the first two weeks after birth than in adult life. In the first two weeks the mixed flora established in the upper respiratory tract is comparable to that of adults, except for the rare occurence in well infants of micro-organisms, such as Klebsiella pneumonia, Hemophilus influenzae, and beta-hemolytic streptococci, often responsible for inflammation of the respiratory tract in older persons.‡

METHODS AND MATERIAL

In the present study, nasopharyngeal swabs were obtained via the oral route from premature newborn infants on the 1st, 3d, 5th, and 10th days of life. Seven per cent

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* Reference 2-5.

† References 6-8.

‡ References 2-4.

horse-blood agar and Sabouraud's agar were used. All premature newborn infants admitted to the two nurseries between March and November, 1953, were included in this study, except for occasional larger ones who remained there only briefly and a few infants in such poor condition that they were left undisturbed. One hundred forty-three infants were studied. One hundred seven were born in the Boston Lying-in Hospital and immediately admitted to the Premature Nursery of that hospital, and 36 were born in the other hospitals or at home and transported at from 1 to 48 hours of age to the premature nursery of the Children's Medical Center.

Shortly before the present study was begun, the former routine use of antibiotics and chemotherapy in the Children's Medical Center nursery had been altered so that one-third of the infants received oxytetracycline (Terramycin), one-third received sulfadiazine and penicillin, and one-third were not treated with antibiotics. The management in any one case was predetermined according to rotation. The administration of antibiotics was started soon after admission. Out of a total of 143 infants studied in both nurseries, 51 received antibiotics; 8 received oxytetracycline; 29,

TABLE 1.—*Number of Cultures in 143 Infants Studied*

Cultures Obtained, Day	120	
	No Antibiotics During Preceding 24 Hr.	Antibiotics
3d.	80	45
5th.	87	33
10th.	97	15

combined penicillin and streptomycin, and 14, combined penicillin and sulfadiazine. Oxytetracycline was given orally in a dosage of 30 mg. per kilogram of body weight per day. The dosages of sulfadiazine, penicillin, and streptomycin were, respectively, 75 mg., 150,000 units, and 75 mg. per day given by injection and divided into three doses. This was continued in the infants at the Children's Medical Center for 10 days and for 4 to 6 days in most instances at the Boston Lying-in Hospital. Bottle feeding or feeding by gavage was begun after 30 hours of age in most instances; in only four instances was feeding begun before the age of 24 hours.

Table 1, which lists the number of cultures obtained from the total of 143 infants in both nurseries, deserves some explanation. For several reasons, the numbers of cultures are not identical on succeeding days. Some of the 120 infants whose throat swabs were cultured on the first day of life died, and in some infants admitted later the first swab was taken on the third day. A few infants were transferred to another department or sent home within the first 10 days of life.

RESULTS

In spite of the dissimilar origins of infants in the two nurseries, there were no significant differences in the nasopharyngeal flora of the two groups. This makes unnecessary any separate presentation of the results for the individual nurseries.

Moreover, the small numbers of infants treated with certain antibiotics (e. g., oxytetracycline) do not lend themselves to statistical comparison. Therefore, all infants treated with antibiotics are considered as one group.

In the cultures of 70.8% of all infants from whom materials for culture were taken during the first 24 hours after birth, no growth was obtained. The number and percentage of the cultures taken during the first 24 hours which showed no growth are presented in Table 2. During the first 12 hours, 75 to 80% of the cultures were sterile, whereas in the age period 19 to 24 hours, the percentage of sterile cultures dropped to 62%. This difference is not statistically significant.

During the first day of life, pyogenic staphylococci were isolated in 14 instances, alpha hemolytic and anhemolytic streptococci in 11, Esch. coli in 8, Neisseria in 2,

TABLE 2.—*Nasopharyngeal Cultures During First Day of Life in 120 Infants*

Hr. After Birth	Total No. Swabs	Sterile Cultures	
		No.	%
0- 6	36	27	75
7-12	20	16	80
13-18	35	24	68.6
19-24	29	18	62
0-24	120	85	70.8

TABLE 3.—*Cultures on Third, Fifth, and Tenth Days of Life*

		No. of Cultures	Pure Cultures	Pure Cultures of Pyogenic Staphylococcus	Incidence			
					Staphylococcus	Streptococcus	Gram-Neg.* Bacteria	Yeast
3d day	No antibiotics	80	45.0%	33.7%	71.2%	30.0%	37.5%	1.2%
	Antibiotics	45	75.5%	51.1%	73.3%	6.6%	42.2%	6.6%
5th day	No antibiotics	87	13.7%	11.4%	83.9%	57.4%	48.2%	13.8%
	Antibiotics	33	69.7%	57.5%	84.8%	33.0%	30.4%	21.2%
10th day	No antibiotics	97	4.3%	4.3%	90.7%	76.2%	55.6%	20.6%
	Antibiotics	15	53.3%	53.3%	93.3%	13.3%	33.3%	33.3%

* Gram-negative bacteria included Esch. coli, Ps. aeruginosa, a few Neisseria, S. marescens, and H. influenzae.

Pseudomonas aeruginosa in 2, and Corynebacterium pseudodiphtheriticum, H. influenzae, and Serratia marcescens, each in 1 instance. In one premature infant, a pure culture of H. influenzae was isolated from the swab taken at two and one-half hours after birth. On the third day other bacteria were present, but H. influenzae was still the predominating micro-organism. From then on there was a gradual elimination, so that at discharge, at 8 weeks, H. Influenza could no longer be isolated. This infant was not treated with antibiotics and had an uneventful course. The swab from another infant which grew S. marcescens also contained Esch. coli. Serratia was cultured from every one of five swabs from this infant, including the one taken on the 16th day of life, or one day before discharge.

The findings on the cultures taken on the 3d, 5th, and 10th days are presented in Table 3. The frequency of pure cultures was higher in the group of infants with antibiotic therapy than in the group without treatment, regardless of the day studied. The incidence of pyogenic staphylococci was the same in the two groups; the incidence of streptococci was significantly reduced by the administration of antibiotics.

Thus, most of the pure cultures were of pyogenic staphylococci. Yeasts were isolated more frequently and Gram-negative bacteria less frequently from the nasopharnyx of the infants on antibiotic therapy, but these differences are not statistically significant.

In successive cultures, pneumococci were isolated from the nasopharynx of three infants, and beta hemolytic streptococci were also found in three infants at two or three examinations. None of these premature newborn infants had signs of an inflammatory process, and none of them had received antibiotics.

Nineteen infants died; 11 on the first day, 2 on the second, three on the third, and 1 on the eighth day. Seven of these premature infants were treated with antibiotics starting shortly after birth. Infection was considered to be the cause of death of only one infant. This child was first given antibiotics at 6 days of age, when he showed definite clinical signs of infection of the respiratory tract. He died two days later. The culture on the first day of life had been sterile; on the third day it had grown anhemolytic streptococci and nonpyogenic and pyogenic staphylococci, and on the fifth day, alpha hemolytic and anhemolytic streptococci, pyogenic staphylococci and nonstaphylococci. Since this represents the normal nasopharyngeal flora, the specific agent of the infection remains unknown. Postmortem examination was not permitted. Postmortem examinations of 11 and clinical evidence in the other 7 infants who died led to diagnosis of prematurity, atelectasis, intracranial hemorrhage, pneumothorax, or combinations of these, as causes of death.

COMMENT

In the past experience at the Premature Nursery at the Children's Medical Center, introduction of routine administration of antibiotics apparently brought about a substantial reduction in mortality.[1] Another alteration in management of premature infants was simultaneously introduced by the substitution of individually air-conditioned incubators for the former cubicle care. Unfortunately, therefore it is impossible to be sure how much of the reduction in mortality resulted from the antibiotics alone. Continuation of the present program, under which every third infant admitted to that nursery becomes an untreated control, should settle this point. That considerable time will be required is suggested by the fact that during the eight months of the present bacteriological investigation no infant in that nursery, and only 1 of the 143 infants studied in both nurseries, died of infection. Since only about one-third of the 143 infants studied bacteriologically received antibiotics, serious infection was seemingly an uncommon problem during this eight-month period. In addition, the infants treated with antibiotics in the Premature Nursery of the Boston Lying-in Hospital were those particularly likely to be infected. This selection introduces another reason why one cannot draw conclusions as to the effect of these drugs upon mortality in the present series.

Nevertheless, information has been obtained as to the bacteriological effects which may be expected when antibiotics and chemotherapy are given either routinely or to selected premature infants. In the limited case material of this study, these effects occured without conclusive differences, whether a combination of sulfadiazine and penicillin or of streptomycin and penicillin or oxytetracycline alone was administered. They consisted primarily of significant reduction in incidence of streptococci among the aerobic flora of the nasopharynx. On the other hand, the incidence of staphylococci was entirely unaffected. To prove or disprove a significant reduction

of Gram-negative flora would require a larger series of infants. The general trend of the combined changes in bacterial flora would appear to be toward the emergence of pure cultures of staphylococci in the throats of treated infants. Finally, it must be emphasized that, since all infections of premature infants are not necessarily bacterial, the nasopharyngeal cultures can seldom give decisive evidence as to treatment or prophylaxis in premature infants, whatever the drugs used.

SUMMARY

Nasopharyngeal cultures have been made on the 1st, 3d, 5th, and 10th days after birth in a group of 143 premature infants in two nurseries. One nursery admits infants directly after delivery in the same hospital; the other admits infants born in other hospitals or at home. In 51 of the infants studied culturally, either penicillin and streptomycin, penicillin and sulfadiazine, or oxytetracycline (Terramycin) alone were administered prophylactically (though in therapeutic doses) during most of the 10-day culture period. The major bacteriological findings were as follows:

1. No significant differences in bacterial flora appeared between the infants in two nurseries.

2. Seventy per cent of all cultures obtained on the first day were sterile.

3. Pyogenic staphylococci predominated in the cultures taken on the third day and thereafter, with alpha hemolytic and anhemolytic streptococci and Gram-negative organisms (largely E. coli) appearing next in frequency. The occasional presence of other organisms is presented.

4. In the limited number of cases given antibiotics, no significant bacteriological differences were obtained between effects of the individual or the combined agents used. The one statistically significant characteristic of nasopharyngeal flora in the entire group of treated infants was reduction in presence of streptococci.

5. The emergence of pure culture of pyogenic staphylococci was noted in those infants treated with antibiotics.

Dr. Harry Shwachman and Dr. Clement Smith suggested and assisted in this study.

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Case Reports

CONGENITAL ALKALOSIS WITH DIARRHEA

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DIARRHEA usually causes metabolic acidosis. The following case is reported because apparently it represents the third patient to be reported with diarrhea and metabolic alkalosis. Two similar patients have been reported.* The present case resembles those previously reported in almost all details.

REPORT OF CASE

The patient, a baby boy, was born in another hospital on Sept. 4, 1952, after an eight-month pregnancy. The birth weight was 5 lb. 9 oz. (2,520 gm.). The parents were of Anglo-Saxon

TABLE 1.—*Studies of Renal Function*

Date	Sp. Gr.	Albumin	WBC	RBC	Casts	BUN	Comment
12/ 9/52	1.008	0	0	0	0	17.0	.....
12/24/52	.....	0	0	0	0	....	.....
12/27/52	.....	0	0	0	0	19.0	.....
1/ 3/53	.....	0	0	0	0	21.0	.....
1/16/53	.....	0	0	0	0	28.0	.....
3/ 9/53	.....	0	Rare	++	0	38.0	2 urine cultures sterile
3/17/53	1.017	0	Rare	++	0	38.0	I.V.P. normal
4/15/53	1.020	0	Rare	Rare	Rare	48.0	Urine culture sterile
6/ 9/53	.....	..	..	..	..	22.0	.....
8/14/53	.....	..	..	..	..	55.0	.....

extraction and were not related. The father died accidentally at the age of 23, shortly after the birth of the patient. The mother, aged 21, was well but was of low intelligence. One older sibling was well. One sibling died shortly after premature birth. There was no history of a similar illness in any relatives.

The baby was breast-fed for the first three weeks of life, but from birth had seven to eight watery stools daily. He was admitted to the local hospital at 3 weeks of age because the weight had dropped to 4 lb. (1,810 gm.). During the subsequent hospitalization, he failed to gain weight, although he took adequate amounts of various formulas. He had 10 to 15 watery stools daily. During this period, he received parenteral fluids of unknown composition. He was admitted to the Pediatric Service of the North Carolina Baptist Hospital on Dec. 9, 1952, at the age of 3 months, for further study. The baby was dehydrated, poorly nourished, and underdeveloped. The weight was 4 lb. 12 oz. (2,155 gm.). The length was 19½ in. (49.5 cm.). The respective circumferences of the head and chest were 12½ and 11 in. (31.8 and 27.9 cm.). The physical examination revealed no specific defects.

He was observed in the hospital for one period of two months and another time for nine days. He was seen sporadically as an outpatient during the subsequent year. The course up to the present time has been characterized by persistent diarrhea and marked retardation of growth and development. At 15 months of age, his height was 27 in. (68.6 cm.), and the circumference of the head was 16 in. (40.6 cm.). The fontanelle was closed. He did not sit alone and had little contact with his environment.

From the Department of Pediatrics of the Bowman Gray School of Medicine of Wake Forest College and the Pediatric Department of the North Carolina Baptist Hospital.

* References 1 and 2.

Laboratory Examination.—The hemogram showed only a mild normochromic normocytic anemia. The total serum proteins were 7.4 gm. per 100 cc. The serum calcium was 11.3 mg. per 100 cc.; phosphorus was 8.5 mg. per 100 cc. The 24-hour excretion of 17-ketosteroids was

TABLE 2.—*Levels of Carbon Dioxide Combining Power, Chloride, Sodium and Potassium*

Date	CO_2 C.P., mEq./L.	Cl	Na	K	Weight, Lb.-Oz. (Gm.)	KCl Therapy
12/ 9/52	35.5	55.8	131.2	2.3	4-12 (2,155)	I.V. Ringer's and D_5H_2O
12/11/52	31.0	85.4	127.0	2.5	4-15 (2,240)	Oral KCl, 10 mEq./day
12/13/52	....	....	.....	...	5-3½ (2,370)	
12/15/52	24.0	80.0	143.5	3.8	5-6 (2,440)	
12/17/52	....	....	.....	...	5-6½ (2,450)	
12/19/52	....	....	.....	...	5-8½ (2,510)	
	33.7	69.0	.....	...		
12/21/52	....	....	.....	...	5-10 (2,550)	
	36.4	74.0	130.5	2.7		Oral KCl stopped
12/23/52	....	....	.....	...	5-10	NaCl clyses started
12/25/52	....	....	.....	...	5-14 (2,665)	
12/27/52	39.1	77.5	135.0	4.0	5-13 (2,350)	
12/29/52	....	....	.....	...	5-12½ (2,620)	
12/31/52	44.0	67.6	.....	...	5-13	Parenteral KCl, 12 mEq./day
1/ 2/53	....	....	.....	...	5-11 (2,580)	Parenteral KCl, 12 mEq./day
	28.4	80.4	133.0	4.25	.....	Parenteral KCl, 8 mEq./day
1/ 4/53	....	....	.....	...	5-15 (2,695)	Parenteral KCl, 8 mEq./day
1/ 6/53	....	....	.....	...	6-5½ (2,880)	
1/ 8/53	....	....	.....	...	6-8 (2,950)	
	31.0	87.4	.....	...		
1/10/53	....	....	.....	...	6-11 (3,030)	Oral KCl, 10 mEq./day
1/12/53	....	....	.....	...	6-12 (3,060)	
1/14/53	....	....	.....	...	6-12	
1/16/53	31.0	82.0	133.0	3.1	6-14 (3,120)	
1/18/53	....	....	.....	...	7-0 (3,175)	
1/20/53	....	....	.....	...	6-14	
1/22/53	....	....	.....	...	6-14½ (3,135)	
1/24/53	....	....	.....	...	6-13 (3,090)	
1/26/53	34.6	72.0	140.5	2.5	6-12	Parenteral KCl, 10 mEq./day
1/28/53	....	....	.....	...	6-12½ (3,075)	
1/30/53	....	....	.....	...	6-11 (3,030)	
2/ 1/53	....	....	.....	...	6-14 (3,120)	
2/ 3/53	....	....	.....	...	7-0 (3,175)	
2/ 5/53	....	....	.....	...	7-3 (3,260)	
2/ 7/53	....	....	.....	...	7-4 (3,290)	
2/ 9/53	32.8	80.7	139.0	3.7	7-5 (3,320)	
2/11/53	....	....	.....	...	7-7 (3,315)	
2/13/53	....	....	.....	...	7-9 (3,430)	
2/15/53	....	....	.....	...	7-12 (3,515)	Parenteral KCl, 7 mEq./day for 2 wk.
3/ 9/53	....	....	.....	...	8-10 (3,710)	No KCl from 3/1-3/9
	29.3	78.6	139.0	3.1	.....	Oral KCl, 10 mEq./day
3/11/53	....	....	.....	...	8-11 (3,940)	
3/13/53	....	....	.....	...	8-11	
3/15/53	....	....	.....	...	9-0 (4,080)	Oral KCl, 10 mEq./day from 3/16-4/15
3/17/53	35.5	80.0	135.0	4.0	9-4 (4,195)	
4/15/53	38.2	....	.....	...	11-3 (5,075)	No KCl
6/ 9/53	53.0	49.0	131.1	2.4	11-2 (5,045)	Oral KCl, 35 mEq./day
7/11/53	39.1	61.9	.....	...	10-9½ (4,805)	Oral KCl, 24 mEq./day
8/14/53	38.2	72.0	136.0	2.8	11-2	

0.17 mg. One serum pH was 7.48. The serologic tests for syphilis were negative. The intradermal reaction to old tuberculin was negative. Cultures of the stools failed to show pathogenic organisms. Microscopic examination of the stool failed to reveal excess fat, white blood cells, or red blood cells. Stool digested x-ray film up to 1/10. Several electrocardiograms were interpreted as being compatible with hypokaliemia. The studies of renal function were difficult to interpret

and are shown in Table 1. He has had azotemia without other evidence of renal insufficiency or inflammation. Three urine cultures were sterile. There was prompt renal excretion of iodopryacet (Diodrast), and the renal architecture was normal. The significance of the azotemia was not clear. The urine pH was always greater than 7.0.

The serum levels of sodium, potassium, chloride, and carbon dioxide combining power are found in Table 2.

Four short-term stool and urine collections were made. Inadequate facilities prevented long-term studies. These data are found in Table 3. The extraordinary excretion of sodium and potassium in urine and stool in the fourth collection cannot be explained by an analytic error. The interesting findings are the excretion of chloride in the stool and excretion of potassium

TABLE 3.—*Data on Short-Term Stool and Urine Collections*

		Na	K	Cl	
I 12/24/52	Intake, estimated	9.96	17.4	9.13	
	12-hour-collection				
	Stool	3.14	1.12	4.5	Stool volume, 31.7 gm.
	Urine	0.9	1.33	0.05	Urine volume, 39.1 ml.
	Output	4.04	2.45	4.55	
	Balance, estimated	5.92	15.0	4.58	
	Balance, mEq./kg./day	4.6	10.8	3.50	
II 2/2/53	Intake, estimated	15.6	33.3	20.3	
	12-hour-collection				
	Stool	4.88	8.52	14.1	Stool volume, 92.0 gm.
	Urine	0.48	5.5	0.02	Urine volume, 44.0 ml.
	Output	5.36	14.02	14.12	
	Balance, estimated	10.24	19.28	6.18	
	Balance, mEq./kg./day	6.0	11.2	3.6	
III 3/10/53	Intake, estimated	34.0	59.4	31.1	
	24-hour-collection				
	Stool	13.16	7.82	27.8	Stool volume, 169.0 gm.
	Urine	3.86	18.10	0.41	Urine volume, 168.0 ml.
	Output	17.02	26.02	28.21	
	Balance, estimated	17.0	33.38	3.9	
	Balance, mEq./kg./day	4.3	8.45	1.0	
IV 3/16/53	Intake, estimated	47.6	96.3	55.7	
	24-hour-collection				
	Stool	40.4	25.0	30.2	Stool volume, 196.0 gm.
	Urine	38.2	122.2	0.21	Urine volume, 339.5 ml.
	Output	78.6	147.2	30.41	
	Balance, estimated	−31.0	−51.9	15.3	
	Balance, mEq./kg./day	− 7.4	−12.1	− 3.6	

in the stool and urine at a time when the serum levels of both ions were low. It would seem that there is a net retention of potassium, although there is persistent hypokaliemia.

The volume of distribution of K^{42} was found to be 38.8 mEq. per kilogram of body weight. Studies by this method have not been done in infants. The value is lower than comparable data in adults and is considerably lower than data in infants found by body analysis.[3]

COMMENT

There seemed to be remarkably little correlation between the clinical status and the biochemical findings. The child seemed to be more vigorous and had a better appetite when he was receiving additional KCl. Parenteral KCl seemed to be more efficacious than oral KCl. As can be seen in Table 2, he gained weight better when receiving additional KCl. Here it seems fairly definite that parenteral KCl was more effective. Oral KCl failed to keep the CO_2 combining power and the serum chloride at levels which were attained when KCl was given parenterally. This obviously suggests that there is some defect in the intestinal absorption of potassium.

This does not explain the failure of renal conservation of potassium. The renal excretion of potassium in the face of hypokaliemia may be related to the obligatory excretion of cations in the presence of alkalosis. No data were obtained pertaining to intracellular composition. It would appear that this syndrome is probably another example of an inborn error of metabolism.

SUMMARY

A case is reported of a baby boy who had congenital chronic diarrhea with alkalosis, hypokaliemia, and mental retardation. Administration of potassium chloride improved his biochemical status but did not completely correct it. The data suggest that the defect may be intestinal absorption of potassium.

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FERROUS SULFATE POISONING

A Nonfatal Case

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FOR MANY years, iron, particularly the ferrous form, has been used as a medicinal agent in nutritional anemia and prepartal management. Since ferrous sulfate is relatively inexpensive, quite stable, not unpalatable, and, up to 1947, considered quite harmless, it has enjoyed wide distribution and in tablet form has been dispensed in large numbers with some abandon. This has resulted in easy availability and all too often accidental ingestion by the exploring and inquisitive infant or child.

Forbes,[1] in 1947, described postmortem findings in two cases. Thomson,[2] Prain,[3] Thomson,[4] and Smith [5] further documented the clinical and postmortem features of this condition. Spencer,[6] in 1951, reviewed the various problems involved and noted in Great Britain the beginning of branding procedures to the extent that "the drug is dangerous to young children." Duffy and Diehl [7] and Swift and collaborators [8] further established the clinical and postmortem picture. Veeder,[9] in 1952, reviewed 16 fatal and nonfatal cases and reemphasized the necessity for keeping iron preparations out of reach of infants and young children. Branch [10] reported a fatal case in a 29-month-old child, with death occurring four and one-half hours after the ingestion of ferrous sulfate tablets. Shoss,[11] early in 1954, reported a severe but nonfatal case of ferrous sulfate poisoning treated with dimercaprol (BAL).

REPORT OF CASE

J. M., a 13-month-old Negro girl, was first seen and admitted to the Cook County Hospital at about 6 p. m. on Nov. 11, 1953. The informant stated that approximately three hours prior to admission the infant was believed to have ingested between 20 and 30 tablets of a preparation that had been dispensed at a prenatal clinic. Identification was established as 3-grain (0.19 gm.) ferrous sulfate tablets. One-half hour to 45 minutes after ingestion, the infant began to retch and vomited some blood-stained material. Soon thereafter, she became increasingly drowsy and lethargic, and began to perspire freely; she was then brought to the hospital.

Physical examination disclosed a well-nourished Negro infant, obviously appearing acutely ill and mildly cyanotic, sweating, and in shock. Rectal temperature was 37.4 C. (99.3 F.); blood pressure, 76 systolic, 42 diastolic; respirations, 36 per minute, shallow, and labored; pulse, 156 per minute but strong. Dried crusts of blood were observed in both nares, on the tongue, and on the chin. The pupils were equal, somewhat constricted, and reacted to light. The neck was supple, but the patient responded very poorly to painful stimuli. A marked hypotonia and hyporeflexia were noted. Examination was otherwise negative, and the past history and family history were noncontributory.

The patient was promptly lavaged with copious amounts of sodium bicarbonate solution, and a considerable quantity of a thick viscid brownish red material was recovered, which contained one or two partially dissolved and fragmented tablets. Serum iron determination at this time was found to be 1.68 mg. per 100 cc. In our laboratories, the low normal range is 0.056 mg. and the high normal range, 0.168 mg. Other determinations at this time revealed NPN 36 mg., inorganic phosphorus 5.9 mg., icteric index 6, albumin 3.8 gm., globulin 2.2 gm., cholesterol, 228 mg., alkaline phosphatase, 7.9 Bodansky units; cephalin flocculation 0, and thymol turbidity 4.1 units. No methemoglobin determinations were made. The patient was given 250 cc. of

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whole blood and oxygen and maintained in a warm bed. After the transfusion, 500 cc. of 5% dextrose in water was administered intravenously. Penicillin and vitamin K therapy were started in appropriate dosages.

During the night, she had one large semiliquid tarry stool and an occasional small emesis of a greenish blood-stained viscid substance. The infant remained lethargic. On the following morning, there was considerable improvement. She was alert and active, with comfortable respirations and a strong regular pulse of 136 per minute. The rectal temperature was elevated to 38.7 C. (101.7 F.) but returned to normal within 24 hours and remained normal for the rest of the hospital confinement. Improvement was steady and continuous, and no evidence of a relapse was noted, as has been so frequently described in this type of poisoning. Serum iron determinations on the second, third, and fourth days of hospitalization were all within normal limits. Bone marrow studies, urinalysis, bleeding and clotting times, serologic reactions, Mantoux reaction (1:10,000), roentgenograms of the chest and long bones were essentially normal and noncontributory. A repeat liver profile on the seventh hospital day demonstrated no abnormalities. A hemogram 18 hours after admission showed hemoglobin, 80%; RBC, 4,670,000; WBC, 20,200, with a differential count of 40% polymorphonuclears, 20% bands, 1% eosinophiles, 30% lymphocytes, and 9% monocytes. The platelet count was not abnormal. Four days after admission, the hemogram revealed hemoglobin, 70%; RBC, 4,840,000; WBC, 11,050, with 12% polymorphonuclears, 1% bands, 2% eosinophiles, 75% lymphocytes, and 10% monocytes.

The infant was discharged eight days after admission, apparently completely recovered.

COMMENT

Since the report of Forbes,[1] in 1947, an increasing number of cases of ferrous sulfate poisoning have been documented in the literature. The clinical picture of vomiting, lethargy, shock, gastrointestinal hemorrhage, and high mortality has been amply emphasized. Early and aggressive therapy to combat the shock and collapse is essential. Relapses are to be anticipated, and when they occur, appropriate measures are to be taken.

A recommendation is advanced for adequate branding of the drug as a potential poison.

SUMMARY

A case of ferrous sulfate poisoning with recovery in a 13-month-old infant is reported. Laboratory data of serum iron determinations are presented to substantiate the diagnosis. Through December, 1952, at least 26 cases of ferrous sulfate poisoning have been documented.

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GALL BLADDER DISEASE IN A SEVEN-AND-ONE-HALF-YEAR-OLD CHILD

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GALL BLADDER disease is generally admitted to be very uncommon in childhood. As in adults, the cause is obscure. The commonest cause of cholelithiasis in childhood. according to Ladd and Gross,[1] is related to the excessive excretion of pigments during a hemolytic anemia. Typhoid is considered a likely cause, and respiratory infections, scarlet fever, and measles in childhood have also been implicated, at least as the forerunners of an attack of cholecystitis. Considering the frequency of respiratory infections in childhood and the rarity of gall bladder disease in this age group, it seems unlikely that respiratory infection plays the sole causative role without some other factors operating. One of these may be agglutinins in the bile. According to the experiments of Sterling,[2] agglutinins appear in the bile of dogs in response to a specific infection, and through their ability to cause agglutination or precipitation, a nidus for stone growth develops. He found that the gall bladder bile contained agglutinin in every one of 12 adult patients with calculi. In patients without gallstones only agglutinin to Escherichia coli was present in the gall bladder bile of one of six patients.

In 1952, Ulin, Nosal, and Martin [3] made a careful critical analysis of gall bladder disease in childhood reported up to 1948. They state that:

> The general trend of the information collected seems to indicate that infection, locally and systemic, plays a more important part in childhood cholecystitis than in that of the adult. Jaundice in most of the cases in childhood is due in some way to an acute inflammatory process adjacent to or involving the ducts and not the common duct stone.

In order to further alert physicians to the possibility of gall bladder disease in childhood, the following report of this disease in a 7½-year-old child is presented.

REPORT OF CASE

N. L., a white girl 7½ years of age, was admitted to the pediatric department of the Northern Division of the Albert Einstein Medical Center on Jan. 20, 1953, because of a skin rash, vomiting, diarrhea, and high fever. Two days before admission she complained of a stiff neck and had a temperature of 101F. The family physician found pharyngitis and gave her 300,000 units of penicillin procaine I.M. About two hours after the injection of penicillin, a morbilliform rash appeared. Previous injections of penicillin had caused no untoward effects. With the onset of the rash, persistent vomiting of a watery colorless fluid occurred. Twenty-four hours later, diarrhea also developed.

P. M. H.—She was a full-term infant, born in a normal manner. Icterus neonatorum did not develop. After some feeding difficulty during the first month, she gained regularly and developed normally. Immunization procedures were carried out during the first year. She had chicken pox at 5 years of age, measles and pyelitis at 6 years. There was no history of any

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blood dyscrasia either in the patient or her family. Since the age of 3 years she had episodes of abdominal pain about four or five times a year. They usually lasted 10 to 15 minutes and disappeared without treatment. They were never accompanied by nausea, vomiting or diarrhea, and icterus was never noticed. Three months before admission, for a short period she complained of abdominal pain and nausea every morning after breakfast. It ceased when eggs were not given at this meal. They were subsequently removed entirely from her diet because they seemed to upset her. The family history is not relevant.

On admission she was well nourished and well developed, but extremely toxic, with a temperature of 105 F. A morbilliform rash was present on the neck, chest, abdomen, and extremities. The skin also appeared slightly icteric. The conjunctivae were congested. The lips were dry, the tongue coated, and the pharynx congested. No pathology was demonstrable on physical examination of the heart and lungs. The abdomen was not tender on palpation, and no masses were felt. The liver edge was just below the costal margin. The reflexes were normal, and meningeal signs were absent. The blood pressure was 100/50 mm. of Hg.

She was placed in an oxygen tent, in which she remained for six days. Elixir diphenhydramine (Benadryl) was given by mouth every six hours for two days because of the rash, which was thought to be due to an allergic reaction to penicillin. The rash disappeared in two days and seemed to be unaffected by the diphenhydramine. For the first two days, she was able to retain an occasional feeding. Persistent vomiting of a bile-stained material then occurred. Liquid brown bowel movements continued two to three times a day. They were not acholic, and blood was not grossly evident. All oral food and medication had to be discontinued. Because of the high polymorphonuclear leucocytosis, oxytetracycline (Terramycin), 300 mg. I.V. every 12 hours, was given to combat infection. Ascorbic acid, 100 mg. I.V., also was given once daily until she was able to retain it by mouth. Intravenous administration of dextrose, at first 5% and later 10% in water, was started.

On the second day after admission, nuchal rigidity and Brudzinski signs were present. A lumbar puncture yielded a clear spinal fluid which was found to be normal on laboratory examination. The meningeal signs were interpreted as due to a meningismus associated with the toxemia. Icterus was more marked. At this time there also developed pain in the upper abdomen which was not well localized by the patient. Although the patient was extremely uncooperative, the abdomen was found on careful palpation to be tender throughout, with very definite rigidity and tenderness over the gall bladder region. By the third day after admission, in addition to the above signs, the liver was palpated two fingers below the costal margin. High fever was still present, and with the increasing toxemia and jaundice, the patient became drowsy and extremely prostrated, so much so that she appeared to be dying. A gallop rhythm had developed, and the blood pressure had dropped to 50/30 mm. of Hg. ECG showed myocardial impairment, and a portable x-ray film of the chest revealed enlargement of the cardiac silhouette.

Since oxytetracycline alone seemed to be ineffective in controlling the infection, streptomycin, 250 mg. I.M. every six hours was given in addition to the oxytetracycline. Protein hydrolysate (Amigen) also was added to the intravenous solution. On the fourth day she received a small transfusion of 100 cc. of blood. A larger amount was not given for fear of taxing the impaired myocardium. Cortisone was started in an attempt to lessen the absorption of toxins through its well-known action of decreasing capillary permeability. The dose was 50 mg. I.M. for two doses at six-hour intervals and then 25 mg. every six hours. Because of the adverse effects that cortisone exerts on infection, the dose of oxytetracycline was at the same time increased to 250 mg. every six hours. On the fifth day, through a misunderstanding, 350 mg. of cortisone was given in divided doses I.M. She also received very slowly a blood transfusion of 250 cc. The next day, the sixth, the child appeared less toxic. The temperature range was lower and the blood pressure more elevated. Vomiting and diarrhea had stopped, and she was able to take a little nourishment by mouth. Gallop rhythm was still present, however, but not as marked. The abdomen was still tender throughout, and there was less pain, tenderness, and rigidity on palpation over the gall bladder region.

On the seventh day, in spite of a persistent high polymorphonuclear leucocytosis, the temperature became normal and gallop rhythm had almost disappeared. The B.P. was 94/54 mm. of Hg. ECG showed less marked myocardial abnormality. Icterus was less, and bilirubin was absent from the urine. Cortisone, which up to this day had been given intramuscularly, was

started by mouth. The dose was gradually reduced and was discontinued on the 10th day. Streptomycin and oxytetracycline, however, were continued for another seven days to prevent any adverse effects of the cortisone.

On the ninth day, no tenderness, pain, or rigidity could be elicited over the gall bladder region. She was well enough to be sent to the x-ray department for a flat plate of the abdomen and chest. The x-ray plate of the abdomen revealed a small cluster of calcific densities located in the right upper quadrant of the abdomen, which could represent gall bladder calculi. The chest was found to be normal.

Improvement continued steadily until the 20th day after admission, when the child complained again of abdominal pain. She had a degree of fever and vomited green-yellowish material. These symptoms continued for 48 hours. It was subsequently found that she had eaten eggs, which, according to her mother, frequently produced these effects.

On the 24th day oral cholecystography was done. It was reported as follows:

"There was no definite visualization of the biliary vesicle at any time during the examination. Two calcified shadows were noted in the right upper quadrant. One of these may represent a calcified gland. The other looks suspicious of a biliary calculus. *Conclusion:* Nonfunctioning gall bladder, most likely containing at least one calculus."

She was discharged on the 28th day to be under the care of her family physician. The latter was instructed to have her readmitted for gall bladder surgery as soon as her condition permitted.

She was readmitted to the hospital on May 18, 1953, three months after she was discharged. While at home she did well except for occasional attacks of abdominal pain associated with nausea. On one occasion she vomited. The pain invariably occurred about one to two hours after meals. Fever and jaundice did not develop. The readmission physical examination showed the child to be well nourished and of good color. No pain or tenderness could be elicited anywhere in the abdomen. The liver was not enlarged, and the spleen was palpable on deep inspiration. The remainder of her physical examination was entirely negative.

The x-ray report after readmission was as follows: "Survey film of the abdomen shows a small radiopaque shadow in the right upper quadrant below the 12th rib. This may represent a calculus within the gall bladder. The liver is not enlarged."

On May 26, a cholecystectomy was performed. Eight hours after operation, the patient showed evidences of an intra-abdominal hemorrhage. The abdomen was reopened, and the bleeding liver bed was sutured. A transfusion of 1,000 cc. of blood was given.

Her condition rapidly improved, and her subsequent course was uneventful. She was discharged 10 days after operation.

PATHOLOGIC REPORT

The gall bladder was narrow and measured 7 cm. in length. There was a slight increase in thickness. The lumen contained thin serous slightly bile-stained fluid. In the fundus there was a small round calculus 4 mm. in diameter which grossly appeared to be composed of pigment and cholesterol. In the ampullary region there was an inspissated calculus. It measured 0.75 cm. in greatest dimension. It was tan, and the surface was composed of numerous small spicules. The calculus was brittle and calcific.

Microscopic.—The gall bladder was the seat of the pathological alterations. The serosa was somewhat thickened. There were numerous dilated vessels and a fine sprinkling of chronic inflammatory cells. The muscularis was similarly hypertrophied. Through the dehiscences in the muscular wall, crypts of surface epithelium (Rokitansky-Aschoff sinuses) could be seen to protrude. The mucosa was edematous. At some points it was denuded. Elsewhere, the mucosal pattern was altered by a flattening change, so that the usual villous appearance was eliminated.

Chemical Analysis of Calculi

Fundus:	Ammonium ion	Positive
	Urate ion or uric acid	Positive
	Calcium (probably carbonate)	Positive
Ampulla:	Fibrin	Positive
	Calcium Carbonate	Positive

Diagnosis.—Chronic cholecystitis; cholelithiasis (calcium carbonate).

COMMENT

One could surmise from reading this case report that the diagnosis of gall bladder disease in this child presented no difficulties. This was not so, however, for the rarity of this disease in children made the pediatrists and the many consultants who examined the child doubt its presence. The patient's complete lack of cooperation added to the difficulties of diagnosis.

The persistent vomiting of bile-stained material during the first few days of illness excluded the possibility of an obstruction in the common duct. Because of the latter, the septic temperature, and the high polymorphonuclear leucocyte count, liver abscess was more seriously considered than either acute cholecystitis or cholelithiasis.

The critical condition of the patient certainly precluded any exploratory surgery. Treatment was mainly directed to the maintenance of adequate hydration and electrolyte balance, the prevention of anoxia, and the combatting of infection. Fortuitously, oxytetracycline was the drug used from the beginning to combat infection. This was perhaps fortunate, since Zaslow,[4] who is studying antibiotics in diseases of the biliary tract, found as a result of recent investigations * that oxytetracycline when given intravenously is excreted from the liver regardless of the degree of liver damage in concentrations which are therapeutically effective. The excretion of penicillin, streptomycin, chlortetracycline (Aureomycin), and the sulfonamides, however, is impaired in the presence of even mild liver damage. The oxytetracycline, however, seemed to be ineffective even with the addition of streptomycin, for the child's course continued downhill until cortisone was administered parenterally in addition to these drugs. The exact mode of action of cortisone in infection is not known. It does not destroy pathogenic organisms or directly influence toxins, allergins, or other specific noxious agents. It seems to alter in some mysterious way certain reactions of tissues to adverse stimuli.

The administration of this hormone is not without danger, however, since it suppresses inflammatory processes that are necessary to combat infections. This danger is minimized, however, by the use of antibiotics effective against the bacteria that cause the infection. According to Kinsell and co-workers [5]:

> There appears to be a definite place for employment of ACTH and cortisone in conjunction with intensive antibiotic therapy in treatment of patients with infections of more than usual severity . . . which fail to respond adequately to antibiotics alone. If hormonal therapy is to be used in such patients, it should be intensive initially, but should be decreased as rapidly as the patient's improvement permits.

The effects of cortisone on this child were excellent, for she promptly became less toxic. The inadvertent administration of 350 mg. of cortisone in a 24-hour period certainly did no harm. In fact, it may have helped the child. Fortunately, the continuous venoclysis of electrolyte solutions and the unimpaired kidney function prevented the electrolyte imbalance that large doses of cortisone produce.

This case report serves to emphasize that while gall bladder disease is known to be rare in childhood, its presence must be seriously considered when symptoms indicating such a possibility are present.

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* Zaslow, J.: Personal communication to the authors.

Laboratory Data

	1st Day	2d Day	3d Day	6th Day	9th Day	20th Day	Readmission
C.B.C.							
Hgb	11.2 gm.	....	9.7 gm.	10.4 gm.	....	11.3 gm.	13.2 gm.
RBC	3,740,000	....	3,140,000	3,620,000	....	4,010,000	5,180,000
WBC	14,950	....	29,700	27,450	20,000	14,000	6,100
Pmn	90%	....	92%	93%	80%	60%	39%
Lymph	9%	....	4%	4%	10%	20%	51%
Mono	1%	....	4%	3%	3%	4%	7%
Eos	0%	....	....	....	1%	1%	3%
Platelets	....	....	....	194,000	....	....	....
Urinalysis							
Bilirubin	+	....	+	....	....	....	Neg.
Urobilinogen	Pos.—diluted	....	....	....	....	....	Pos.—undil.
Culture	....	....	Neg.	....	....	....	....
Sp. gravity	1.025	....	....	....	....	....	1.023
Albumin	Trace	....	+	....	....	....	Neg.
Sugar	Neg.	....	++	....	....	....	Neg.
Acetone	Neg.	....	....	....	....	....	Neg.
WBC	Few	....	Occas.	....	....	....	Neg.
RBC	0.1	....	....	....	....	....	Neg.
Blood culture	Neg. in 10 days	....	Neg. in 10 days	....	....	....	....
Nose and throat culture	Micrococcus catarrhalis; pneumococci; nonhemolytic streptococci	....	....	....	....	....	....
Stool culture	Pseudomonas aeruginosa; Escherichia coli	....	....	....	....	....	....
Agglutination tests							
B. Typhosus O	Neg.	....	....	....	....	....	....
B. Typhosus H	Neg.	....	....	....	....	....	....
B. Paratyphosus A	Neg.	....	....	....	....	....	....
B. Paratyphosus B	Neg.	....	....	....	....	....	....
Lumbar puncture	....	Neg.	....	....	....	....	....
Blood bilirubin							
Direct	....	1.0 mg./100 cc.	....	. ..	....	....	0.2 mg./100 cc.
Indirect	....	2.0 mg./100 cc.	....	....	....	....	0.4 mg./100 cc.
Icterus index	....	....	20 units	....	....	....	....
Thymol turbidity	....	....	12 units	....	....	....	2 units
Serum Na	....	....	142 mEq./L.	....	....	....	....
Serum K	....	....	5 mEq./L.	....	....	....	....
Serum Cl	....	....	90 mEq./L.	....	....	....	....
Serum CO_2	....	....	18 mEq./L.	....	....	....	....
Alk. phosphatase	....	....	4 Bodansky units	....	....	....	5.9 Bodansky units
Total cholesterol	....	....	720 mg./100 cc.	....	....	....	170 mg./100 cc.
Ceph. floc	....	....	....	1+ in 24 hr. 3+ in 48 hr.	....	....	....
B.U.N.	....	....	40 mg./ 100 cc.	23 mg./ 100 cc.	....	....	....
Prothrombin time	....	....	....	Normal	....	....	12 sec. 100% Control 12 sec. 100%
Wintrobe sed. rate	....	....	....	....	17 mm./1 hr.	....	9 mm./1 hr.
RBC fragility (Hypo. saline)	....	....	....	....	....	....	Begins 0.48 Complete 0.34
Total protein	....	....	....	....	....	....	6.5 gm./100 cc.
A./G.	....	....	....	....	....	....	3.7/2.8
Heterophile antibody	....	....	....	....	Neg.	....	....

SUMMARY AND CONCLUSIONS

A case of acute gall bladder disease with overwhelming toxemia in a 7½-year-old child is presented.

The beneficent effects of cortisone in conjunction with intensive antibiotic therapy in an infection of unusual severity is shown.

The rarity of this disease in a particular age group should not blind the physician to its possible occurrence.

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Progress in Pediatrics

RETROLENTAL FIBROPLASIA

Current Notes

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RETROLENTAL fibroplasia is now the commonest late complication of extremely premature birth. Until 15 years ago, blindness from this cause was so rare that the disease was not recognized. Terry,[1] in 1942, wrote the first descriptions of retrolental fibroplasia as an entity and later named the disease.[2] Since that time, the literature about this form of infantile blindness has grown rapidly, and many investigators have sought the nature of the pathology, pathogenesis, clinical manifestations, etiologic factors, and therapeusis of the disease.

HISTORY

We are indebted to Terry not only for first calling our attention to retrolental fibroplasia, but also for pointing out the etiologic factor [3] that has borne the test of time—prematurity. It is now agreed that the greater the degree of prematurity, the greater the incidence of retrolental fibroplasia.[4] Owens and Owens [7] described the clinical pathogenesis of the disease: a vascular phenomenon, characterized by engorgement, hyperplasia, and neoplasia of the retinal blood vessels of the periphery, followed by retinal edema and detachment, leading to glial and fibrous scarring of the retina folded behind the crystalline lens. Krause [8] described the late pathology and made extensive investigations of many potential etiologic factors, as well as social ramifications, of retrolental fibroplasia. Reese,[9] and Heath,[10] and Friedenwald [11] have confirmed Owens' clinical observations of the acute vascular onset of retrolental fibroplasia by histologic study of eyes of premature infants who died with the acute disease. Various methods of treatment have been suggested, but all, including vitamin E,[12] corticotropin (ACTH) [13] and oxygen [14] have been found wanting.

CURRENT INVESTIGATIONS

Growth and Development.—Huggert * has significantly added to our knowledge about the maturation of the vascular system of the human eye. Of infants born weighing less than 2,000 gm., most at birth had embryonal vascular structures and vitreous clouding that disappeared in two to three weeks. Infants born weighing less than 1,601 gm. not only had these embryonal vessels, but frequently had thread-like retinal vessels in the first weeks after birth. These retinal vessels grew in size to normal within five to seven weeks in the smaller and within two to three weeks in the larger infants of the group. Half of these infants with early vitreous clouding

Now on active duty with the United States Navy.
From the Department of Pediatrics, University of Texas School of Medicine.
Presented in part at the annual meeting of the American Academy of Pediatrics, Oct. 21, 1952, Chicago.

* References 15 and 16.

and thread-like retinal vessels later had dilated vessels, either with or followed by peripheral retinal clouding, edema, or, even, detachment and neoplasia. The other half of this group of smaller premature infants proceeded through normal ocular growth without incident. An occasional infant of over 1,600 gm. birth weight had dilated vessels and retinal changes in the 1st or 2d week after birth, in contrast to the smaller infants, who had these troubles begin from the 3d to the 10th week after birth. Two of the smaller infants went on to have cicatricial retrolental fibroplasia, and the remainder of the group of 130 were thought to have normal eyes. Thus, the vascular growth and development of the retinal blood vessels progresses according to an orderly preset pattern more closely related to weight than to age after birth. Fletcher has confirmed and extended Huggert's work.[31]

This growth and maturation process of the retinal blood supply and the apparent need for the presence of a definite stage of ocular development from which retrolental fibroplasia as an acute overgrowth of the blood vessels may begin affords an enticing explanation for the observation that retrolental fibroplasia has its onset according to weight,[17] rather than to any special age in premature infants. The typical weight at the onset of retrolental fibroplasia is 1,800 to 2,200 gm. This weight of onset is as reliable as weight is as an index of prematurity. Practically speaking, the smaller the premature infant at birth, the later the onset of the disease, and vice versa, to the point where intrauterine development has proceeded beyond the susceptible stage of ocular vascular growth. That retrolental fibroplasia is extremely rare in infants born weighing 2,000 gm. or more is well known.[18]

Precipitating Factors.—The factors that disturb the orderly process of growth and maturation of the retinal vascular system and lead to the exuberant extension of normal capillary growth which is retrolental fibroplasia may be many and need be related only by their end-effect.

Oxygen: Crosse,[21] Ryan,[22] and Patz [23] have presented clinical evidence that chronically excessive oxygen concentrations administered to premature infants may increase the incidence of blindness due to retrolental fibroplasia. The smallest premature infants may increase the incidence of blindness due to retrolental fibroplasia. The smallest premature infants remain those most often affected. The possible mechanisms of action are not yet surely understood and may be several.

Campbell's [24] experiments with newborn rats in low-pressure chambers reveal that vascular growth is slower at low oxygen pressures and that the capillary free area around the retinal arterioles is smaller. An adult type of capillary pattern emerges more rapidly in rats kept at low pressures. He postulates that vascularization is governed by tissue oxygen need and points out that retinal vascularization does not begin until atrophy of the fetal system has come. He further postulates that administration of high concentrations of oxygen upsets normal growth processes by producing excessive levels of tissue oxygen saturation. He also points out that the normal site of most rapid vascular growth, the periphery of the human eye, is the site of onset of retrolental fibroplasia.

Gyllensten and Hellström [25] have extended these investigations in the opposite direction by subjecting newborn mice to repeated cycles of 48 hours of 100% oxygen alternated with 24 hours of room air. In one-third of 50 mice so treated, histologic study revealed retinal and vitreous hemorrhage, retinal folds and detachment, and vitreous invasion by new vessels and fibrous tissue, as well as persistence and hyperplasia of the embryonic vascular system.

Gyllensten and Hellström's data along with Campbell's data and postulations lend firm support to the clinical observations by Crosse, Ryan, and Patz of the apparent association of prolonged high oxygen concentration with a high incidence of retrolental fibroplasia in infants with immature eyes.

Electrolytes: The author has shown that the incidence of blindness due to retrolental fibroplasia in the Chicago Lying-In Hospital of the University of Chicago is influenced by the sodium content of the diet.[26] Where cow's-milk formulae containing 20 mEq. or less of sodium per liter were fed, the incidence of blindness due to retrolental fibroplasia was 7 in 103 infants born weighing less than 1,500 gm. Where cow's-milk formulae containing 56 mEq. of sodium per liter were fed, 21 of 48 infants born weighing less than 1,500 gm. became blind from retrolental fibroplasia. In the three years since the sodium content of premature infant formulae at the Chicago Lying-in Hospital of the University of Chicago has been held at a lower figure, the incidence of blindness due to retrolental fibroplasia in infants born weighing less than 1,500 gm. is less than 3%.

After these observations in Chicago, an alternate series was begun at the University of Texas School of Medicine,[27] to prove the apparent influence of salt on the incidence of acute retrolental fibroplasia. Infants born weighing less than 1,500 gm. in roughly matching birth weights, were fed one of two milk formulae which differed only in sodium chloride content. One formula contained an average of 23 mEq. of sodium per liter, while the other had 56 mEq. of sodium per liter. The incidence of retinal detachment due to retrolental fibroplasia was 15 of 17 on the high-salt diet and 4 of 12 on the unadulterated diet. This observation seemed to confirm the previous experience.

Because of the commonness of edema among premature infants, because of their known renal limitations, and because of the frequent use of blood transfusions in premature infants, an experiment was devised to impose some of these conditions on newborn animals with immature eyes. This study has been reported elsewhere in detail.[28] Briefly newborn kittens made chronically edematous and repeatedly given transfusions had ophthalmoscopically persistent vitreous clouding and retinal vascular engorgement, as well as eye lesions histologically similar to the early retinal lesions retrolental fibroplasia in humans.

Blood Transfusions: That intravenous blood transfusions have a place among the various etiologic factors was first indicated in retrospect by Mallek and Spohn.[29] Vitreous and retinal hemorrhage after blood transfusions in premature infants with either the acute vascular lesions of retrolental fibroplasia or sepsis is common.[27] Vitreous hemorrhage complicating acute retrolental fibroplasia has a bad prognosis. In these patients, the disease is strikingly similar to retinitis proliferans.

COMMENT

The blood vessels of the retina of the infant born weighing less than 1,600 gm. are incompletely developed at birth. Rapid vascular growth occurs in a few weeks, to bring the retinal vascular system to a relative state of maturity. Any factor which disturbs this growth impulse so that it is prolonged or exuberant may result in neovascularization, or hyperplasia of the retinal vessels continuing after the stage of maturation. The acute vascular lesion of retrolental fibroplasia then begins as if it were a pathologic extension of normal vascular growth.

Oxygen in high concentrations may be a stimulating factor. The retinal vasoconstrictor effect of breathing pure oxygen and the dilator effect of anoxia in the adult was proved by the retinal photography of Cusick and co-workers.[30] Oxygen lack or excess undoubtedly has an effect on the retinal vessels. High tissue concentrations of oxygen which reduce the demand for vascular growth in its normal site may divert the growth impulse of these vessels into an abnormal location, the vitreous. Vitreous invasion constitutes the first unquestionable stage of retrolental fibroplasia.

Electrolyte intake may be a stimulating factor in that the electrolyte intake may exceed the infant's immature metabolic capacities. In this fashion, retention may lead to increased blood volume, hyperelectrolytemia, and vascular engorgement, as well as edema. These results may well promote abnormal hyperplasia of normally rapidly growing blood vessels.

Intravenous blood transfusions, particularly those of large volume, may exert a similar deleterious effect. Rapid expansion of the blood volume of an already equilibrated, or perhaps even "water-logged," infant is not the same as transfusion of infants in a state of reduced blood volume, as in shock or dehydration. Not only may further distention of the vascular system occur, but retinal and vitreous bleeding may further complicate existing acute retrolental fibroplasia and make worse the prognosis. What part a temporarily sustained hypertension induced by transfusion of the essentially pressoreceptor denervated premature infant may play in producing progression of retrolental fibroplasia or intraocular bleeding has not yet been clarified.

Infections in premature infants may play a part in precipitating acute retrolental fibroplasia in some premature infants. Retinal and vitreous bleeding are not uncommon in premature infants with sepsis, as are electrolyte imbalance, prolonged administration of high concentrations of oxygen, and severe degrees of anemia requiring blood transfusions. A severe infection, then, has the potentiality in a premature infant whose eyes are in the critical stage of development to precipitate the most serious form of retrolental fibroplasia.

RECOMMENDATIONS

On the basis of available information to reduce the incidence of retrolental fibroplasia, it seems justifiable to forward the following recommendations until more exact and better-substantiated data are at hand.

Oxygen tends to be overused, rather than underused, both in concentration and in duration of therapy. After the first two or three days, concentrations greater than 40% are rarely indicated, and after two or three weeks, need for more than room air is uncommon.

Formulae for premature infants are best not adulterated with sodium chloride and should be of less electrolyte concentration than whole cow's milk. Saline injections are rarely indicated and can be replaced by dextrose water for most uses in the management of premature infants.

Intravenous blood transfusions should be made only when sorely needed. The volumes given should be less than 5 ml. per pound (0.5 kg.) of body weight. No intravenous transfusions should be given an infant born weighing less than 2,000 gm.

until a funduscopic examination has determined the presence or absence of retrolental fibroplasia. The presence of retrolental fibroplasia contraindicates transfusions in terms of the prognosis for vision.

SUMMARY

Retrolental fibroplasia is basically a disease of exuberant retinal vascular overgrowth which manifests itself at a definite level of ocular growth and development.

The acute vascular lesion of retrolental fibroplasia may be produced, or made worse when already present, by any factor which overstimulates vascular growth or which causes intraocular bleeding.

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Society Transactions

AMERICAN PEDIATRIC SOCIETY

Rustin McIntosh, M.D., *President*

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Hypernatremia in Infants: An Evaluation of the Clinical and Biochemical Findings Accompanying this State. Dr. Laurence Finberg (by invitation) and Dr. Harold E. Harrison, Baltimore.

This study deals with a correlation of the clinical, biochemical, and pathological findings in 80 infants whose serum sodium concentration exceeded 150 mEq. per liter during their illness. Sixty-seven of these were treated on the Pediatric Service of the Baltimore City Hospitals over a six-year period. The underlying condition responsible for this electrolyte derangement was diarrheal disease in the majority of the cases.

Although this physiological disturbance cannot be diagnosed invariably without laboratory data, it can frequently be suspected from the clinical picture. Very young infants and, particularly, prematurely born infants are those most likely to be involved. The abrupt cessation of fluid intake for a period of 12 to 30 hours prior to admission is an almost constant feature. In some infants a prolonged febrile course suggests that increases in losses of insensible water may play a role. In about two-thirds of those studied there were symptoms referable to the central nervous system, which ranged from marked irritibility with muscular hypertonicity to severe convulsive manifestations and stupor. Twenty-eight out of 30 cerebrospinal-fluid examinations showed an increased protein content. Several of the patients who died had subarachnoid hemorrhage, and a number of surviving patients had severe neurologic residua. Despite the fact that the subsequent course indicated marked reduction of body water volume at the time of admission, almost half of the infants studied did not appear more than slightly dehydrated clinically when first examined. A doughy or "sclerema-like" texture of the skin and subcutaneous tissues, though striking when present, was not a constant feature.

Studies of the serum cations revealed several interesting additional features. Of those patients in whom serum calcium measurements were made, 28 out of 40 showed a significant decrease in serum calcium concentration. In 21 of these patients this was known to have occurred prior to correction of dehydration and acidosis. Symptoms of tetany were sometimes seen after rehydration and correction of acidosis. It seems quite possible that the similar clinical states described as "hyperosmolarity" and "postacidotic tetany" may both be part of the disturbance attributable to increased electrolyte concentrations with the concomitant intracellular dehydration. A small but theoretically interesting group of patients are those whose serum potassium concentrations were decreased initially despite the presence of oliguria and azotemia. Following hydration of these patients, biochemical evidences of potassium deficiency, including metabolic alkalosis and a persistently low level of serum potassium, were marked, and the patient's recovery was slow until correction was effected. Calculations of data from acute balance study on a patient suggested that during initial rehydration the percentage expansion of the intracellular and extracellular compartments was equal, so that about two-thirds of the water retained was held in the intracellular compartment.

The special treatment required by this rather large group of patients with hypernatremia makes it important to assess the commonly employed regimens for treating dehydration. Recognition or suspicion of this condition from clinical signs and rapid laboratory diagnosis is of aid in planning the therapeutic approach.

DISCUSSION

DR. MITCHELL I. RUBIN, Buffalo: It might be interesting to point out some data that Calcagno and I have collected. When dehydration is brought about by water deprivation in small babies, both the plasma sodium and the chloride rise. This is associated with a striking fall in glomerular filtration rate. The excretion of sodium in the urine falls at a rate comparable to the fall in glomerular filtration. The potassium excretion falls equivalently.

In babies studied with dehydration due to diarrhea, where the plasma sodium rises in association with the loss of hypotonic (diarrheal) solutions by the bowel, there was also a striking fall in glomerular filtration rate. Here, again, the sodium excretion in the urine falls comparable to the fall in glomerular filtration rate. In contrast to dehydration brought about by water deprivation alone, however, potassium excretion rises with the fall in glomerular filtration rate to values somewhere between 40 to 50% of the filtered potassium. We assume that the large excretions of potassium in these babies are evidence of tubular excretion of potassium as a result of tissue breakdown in diarrheal disease.

Our data also indicate that with dehydration and fall in the glomerular filtration there is a higher percentage in tubular reabsorption of the filtered water, Na, and Cl. Our data do not explain why in other instances of diarrheal dehydration hypernatremia does not occur.

In most of our infants with severe dehydration and associated hypernatremia, the clinical signs of dehydration were striking, and in many there was an elevation of the plasma protein and hematocrit, to suggest hemoconcentration (presumably extracellular dehydration).

One other point may be of interest. Where we were able to follow the change of glomerular filtration rate in rehydration in the water-deprived babies, in about 90 minutes after giving dextrose intravenously, the glomerular filtration rate returned to normal values; whereas, in diarrheal babies, two of whom were studied, the rise in glomerular filtration rate was much slower, taking 48 hours.

Thus in diarrheal disease there are at least two factors which may be operative in the development of hypernatremia: hypotonic fluid loss in the diarrheal stools and reduced glomerular filtration of Na. Unexplained factors must exist to account for the variable plasma Na levels, for normal or low values may be found in other infants with comparable dehydration.

DR. ALLAN M. BUTLER, Boston: It is always nice when there is evidence that permits the simplification of therapy. It seems, therefore, worth calling attention to the fact that these infants utilized advantageously a solution containing something in the neighborhood of 40 mEq. of sodium per liter. There also is ample evidence in the literature that a solution containing a similar amount of sodium per liter will correct a hyponatremically dehydrated baby. So the utilization of solutions with such a concentration of sodium and appropriate concentrations of other electrolytes seems to be effective therapy, regardless of the hypotonic or hypertonic nature of the dehydration.

DR. ROBERT KLEIN, Pittsburgh: I should like to ask Dr. Finberg two questions, if I may.

First, was this the total experience with diarrhea in this period, because, as I calculate it, somewhat over 25% of your babies were hypertonic. Dr. Tarail and Dr. Bass went over our cases in Pittsburgh, and they found that roughly 10% of our children came in with hypernatremia.

The other question is, did you experience any difference in the clinical response in those who had been given large amounts of saline solutions before they entered? It was our impression that these children responded very much better, and we had, I believe, much less difficulty in their general management and fewer neurological signs. I wonder if you were able to make a distinction between the two groups.

DR. DANIEL C. DARROW, New Haven, Conn.: We can confirm the complications of high sodium concentrations. In one of our infants, the older brother or sister substituted salt for the sugar in a bowl. The child came in with very marked cerebral symptoms, and these persisted for three weeks, but with subsequent complete recovery.

The other point I should like to make is that when Dr. Yannet analyzed the brains of cats subjected to low sodium concentrations, he found that the brain behaved somewhat differently from other tissues. In the other tissues, as you recall, the tendency was, with a drop of sodium, that water entered the cells. In the brain, apparently in response to the low concentration of sodium in extracellular fluids, potassium left the cells.

Unfortunately, we did not study any of the cats or dogs that were subjected to hypertonic conditions. I believe that it might be of interest for someone to follow that up, for the simple reason that the brain is peculiar among the organs of the body in that it is fixed in a cavity which cannot be expanded, so that the amount of water in the brain cavity has to be relatively constant.

For this reason it is difficult for the brain to react to osmotic changes. The only chance for variations in the amount of water in the brain is when there are variations in the content of blood in the capillaries and veins.

DR. LAURENCE FINBERG, Baltimore: I should like to thank everyone for their comments. No further comment was called for by the first discussants; therefore, I will simply answer Dr. Klein's questions.

Dr. Klein asked if this was our total experience with diarrheal disease. In so far as this represents our hospitalized patients, it is, the only exclusion being those cases having very mild diarrhea, in whom there were no electrolyte determinations available.

I might point out that it is the custom at our hospital to admit only very severely sick infants, so that this may very well not represent the proportion that might be seen in other series.

The second question was whether the patients who had received large amounts of salt responded differently from those who had not. In our experience, although the number we had who received large amounts of salt was relatively small, we could detect no differences.

The Pathogenesis and Symptomatology of Hypertonic Dehydration. DR. WILLIAM B. WEIL (by invitation) and DR. WILLIAM M. WALLACE, Cleveland.

A significant number of infants with sudden severe gastroenteritis show a syndrome characterized by deceptively inapparent dehydration, signs of central nervous system depression and dysfunction, and with relatively little evidence of circulatory impairment. Chemical examination of the blood shows an increase in the concentrations of sodium and chloride, metabolic acidosis, and azotemia.

It will be shown that the pathogenesis of this syndrome of water and electrolyte imbalance is to be found in the nature of the ionic exchanges between large bowel contents and blood and in the rate of renal adjustment to abnormal stool losses. In the process of formation of liquid stools, isotonic ileal fluid loses more sodium than water, more chloride than sodium, and gains potassium. Renal compensation, because of its inherent slowness and immaturity in this age group, fails to adjust concentration to the water loss, and the process tends to be a cumulatively disadvantageous one for the infant.

Extracellular fluid remains relatively intact with regard to volume, and the brunt of the dehydration falls on the intracellular fluid. The genesis of the clinical symptoms and signs finds a reasonable explanation in this type of cellular dehydration.

Recognition of infants with this type of disturbance is essential for rational management.

DISCUSSION

DR. SOLOMON A. KAPLAN, Brooklyn: It has been implied that failure of the infant's kidneys to concentrate the urine maximally may be responsible for the development of hypertonic dehydration. Accordingly, we measured the depression of the freezing point of the urine of six of the patients presented here, the specimens having been forwarded to our laboratory by Dr. Weil.

Much to our surprise, we found that three specimens had concentrations of about 1,200 in osmoles per liter. This figure is close to the maximum concentration which the adult kidney is capable of producing after dehydration. It seems unlikely then that the development of hypertonic dehydration is a consequence of the inability of the infant's kidney to reabsorb maximum quantities of water per unit of excreted solutes.

I should like to ask Dr. Weil a question. In adults the occurrence of cerebral vascular accidents and other intracranial lesions is frequently followed by hypertonicity of the serum, especially if the hypothalamic area is involved. Would you comment on the possibility that some of these infants might have had intracranial lesions?

DR. HAROLD E. HARRISON, Baltimore: I believe that Dr. Weil's paper has very nicely complemented or supplemented our work in pointing out some of the mechanisms involved in the development of hypernatremic dehydration. In essence, I feel that there is a fairly good area of agreement, particularly in the fundamental notion that a major part of the water loss has been from the intracellular fluid.

The question of renal compensation has interested us to a considerable extent, because some of the babies, one of whom was shown by Dr. Finberg, have relapsed; and when in relapse, they have tended to show the same pattern of elevation of serum sodium.

One baby has actually been readmitted to the hospital several times, and each time that he has come in with diarrheal disease, he has had a high serum sodium level. The question of a particular renal defect in such a baby becomes important, although we have not been able to demonstrate any renal dysfunction in that infant.

We also have seen a number of children and adults with head trauma or postoperative neurosurgical problems who have had high serum sodium levels. As you know, there is a good deal in the literature about high serum sodium concentrations occurring in patients who have had damage to the anterior portion of the frontal lobes.

In most of the patients in whom we have been able to get good documentary evidence concerning fluid intake, the intake has been low. For example, one child who had a skull fracture and severe head trauma was admitted to the neurosurgical service and remained comatose for over 10 days. She was getting tube feedings of milk as her sole fluid intake in rather limited amounts. As soon as she was transferred to our service and put on a higher fluid intake with salt restriction, the serum sodium concentration came down to normal, and she regained consciousness.

In that case it seemed fairly clear that though she may have had defective renal compensation, at least the primary fault was lack of water intake, and Welt and his co-workers have suggested that the same thing may be true in many of the patients with encephalopathy or head trauma or in those who have had neurosurgical procedures.

I feel, however, that the possibilty of a specific renal tubular dysfunction has not yet been eliminated. The reports from Dr. Weil and Dr. Wallace's group fit in so nicely with our own experiences that we feel quite happy that we have been able to get both of these papers presented on one program.

DR. GILBERT B. FORBES, Rochester, N. Y.: We were interested in trying to develop some criteria by which the house staff might differentiate the hypertonic from the hypotonic baby on admission to the hospital. Although our experience is very limited, we do have a small experience to report, namely, five infants during the last season with serum sodium concentrations above 150 mEq. per liter, contrasted with five additional infants with serum sodium concentrations below 130 mEq. per liter.

Analysis of the histories as far as intake was concerned revealed no striking differences between these two groups. Data concerning the hypertonic infants (most of them) gave evidence of poor peripheral circulation in contrast with the data which have been reported today.

There was one other difference, one real difference, shall we say, and that was that the hypertonic infants tended to have severer hyperpnea than the the babies with low serum sodiums.

None of our patients had central nervous symptoms which could not be attributed to the loss of water and salt.

The age of the patient was the most helpful thing in our experience, since all the babies with high serum sodiums were below one year of age, and all the babies with low serum sodiums were above one year of age. Aside from this, we could not detect any definitive clinical signs which might help the house staff in making this differential diagnosis.

DR. WILLIAM M. WALLACE, Cleveland: If you reflect on what happens to babies with diarrhea who become dehydrated, you wonder why more of them do not become hypertonic. The fluid losses from the gastrointestinal tract, as well as from the skin and lungs, all hypotonic. However, most infants coming into the hospital with dehydration have apparently been able to maintain a normal serum sodium concentration. Presumably, in this isotonic group dehydration has developed at a rate allowing for adequate renal compensation.

The clinical story seen in babies with hypertonic dehydration is often a catastrophic one. Stool losses have been large and their onset rapid. There is often a history suggestive of excessive insensible water loss. It is not surprising that renal compensation has not been able to keep pace with the excessive and rapid abnormal losses.

At the risk of being accused of frank teleology, one might argue that the hypertonic pattern of the dehydration may have a certain physiologic utility. If complete renal compensation had been made so that extracellular concentrations were adjusted to normal, then transfer of intracellular water to the extracellular space would not have been as effectively carried out, and reduction of extracellular fluid volume might have been so great as to have been lethal. The observation that rapid adjustment of the abnormal concentrations by infusion of very hypotonic solutions frequently leads to worsening of the clinical state indicates that the initial equilibrium is the most optimal one that could have been attained under the given set of circumstances.

DR. BENJAMIN KRAMER, Brooklyn: At the International Pediatric Congress in Habana, Cuba, Dr. Fanconi presented a series of cases of hyperelectrolytemia, due mostly to a high concentration of sodium and chloride. This condition was not the result of diarrhea but was associated with gross brain lesions, which, for the most part, were located either at the base of the brain or in the cerebellum. The hyperelectrolytemia disappeared when a low-salt diet was given or when the lesion was removed by surgery.

DR. GEORGE M. GUEST, Cincinnati: I should like to call attention to another important factor in the pathogenesis of hypertonic dehydration, namely, "insensible" water loss. In studies of dehydration associated with acidosis, attention is usually directed mainly to renal factors; but the loss of water vapor from the lungs associated with hyperventilation is far greater than is generally realized. Recently, Dr. Brodsky and Dr. Miley reported studies done at Louisville bearing on this point. In dogs with experimentally induced acidosis, they found that the rate of insensible weight loss was nearly quadrupled compared with the normal rate. The ventilatory water loss was estimated to be more than twice the amount of water going out of the body in the urine.

DR. CHARLES U. LOWE, Buffalo: Dr. Mitchell Rubin indicated, on the basis of his studies, that the glomerular filtration rate falls significantly in dehydrated patients with diarrheal disease. Dr. Weil, on the other hand, has indicated that the extracellular volume remains constant in such patients. I wonder, therefore, if he would care to speculate on the pathogenesis of the renal dysfunction which he described.

DR. SAMUEL Z. LEVINE, New York: Dr. Guest mentioned the work of Dr. Brodsky. I believe that it is well known that in infants—young infants—the extrarenal water loss, including the loss through the skin and lungs, is about 35 to 40% of the total water output during the day. He also mentioned that it was of low isotonicity.

For the sake of the discussion, is it conceivable that in these hypernatremic persons exposure to a cold environment might produce the hypotonic water loss in the skin and lungs, which might produce the hypernatremia?

DR. ALEX J. STEIGMAN, Louisville: I was prompted to make my comments in view of Dr. Levine's question. We have seen three infants this past year with severe measles encephalitis in whom hypernatremia appeared. We ascribed this to water loss through the lungs, abetted by the hyperpyrexia.

Two of these patients were treated with a phenothiazine derivative (Chlorpromazine) (which has a hypopyretic effect) and the external application of cold, without the administration of fluid, for fear of inducing convulsions. We were gratified to find that the hypernatremia responded very promptly.

DR. ROBERT J. MCKAY JR., Burlington, Vt.: In line with the remarks of the last few discussants, we have had an interesting clinical observation, namely, that our patients whom we have observed with this condition tend to have a history not of oliguria but of anuria during the 12 to 24 hours preceding admission, in many instances regardless of fluid intake.

DR. WILLIAM B. WEIL, Cleveland: I wish to thank all the discussers for their comments, and I should like to thank Dr. Kaplan for the determination of the osmolarity of the urine samples. In regard to the osmolarities, I might add that the patients whose urines were of greatest osmolarity were the ones who clinically improved fastest.

With reference to several of the comments about the role of the central nervous system, I might point out that three of the children with hypertonic dehydration, as a result of gastroenteritis, were mentally retarded. Two other children had primary disease of the central nervous system without gastroenteritis—one was a premature baby with a cerebral hemorrhage and the other a 4-year-old child with a craniopharyngioma and a picture-like diabetes insipidus.

One unusual patient had neither central nervous system disease nor gastroenteritis, but was being fed through a gastrectomy tube because of a lye burn of the esophagus. This child's only fluid intake was a high-protein tube feeding. In addition, she was losing all her saliva through an esophageal cutaneous fistula. She was apparently just maintaining homeostasis, for when she developed an extensive weeping eczematoid skin lesion, she was no longer able to remain compensated in spite of a highly concentrated urine. We were called in consultation and found that her BUN was 188 mg. per 100 cc. and Na was 180 mEq. per liter. The urine was maximally concentrated but contained only 17 mEq. per liter of Na. In spite of parenteral therapy, the child died within 24 hours.

With regard to Dr. Levine's suggestion about a cold environment for these patients, it is interesting to note that in one of our children we felt that sweat losses were an important factor, because this child became ill during a very hot spell last summer, with daily environmental temperatures of 100 F.

Thus, large water deficits can occur in many ways; but in gastroenteritis, stool losses cannot be ignored.

In reply to Dr. Guest, we had one infant with metabolic acidosis and hyperventilation with no known cause. With regard to the experimental acidosis produced by Dr. Brodsky in dogs, only those whose acidosis was produced rapidly by the infusion of hydrochloric acid showed increased extrarenal water loss; the animals made acidotic slowly with ammonium chloride did not show this phenomenon.

Dr. Lowe's question about the cause of the supposed renal dysfunction when the extracellular fluid volume is normal is not easily answered. We might raise two possibilities: The functional plasma volume could be reduced, or the renal impairment in hypertonicity could be similar to that noted in experimental hypotonicity when extracellular fluid is maintained.

Incidentally, I should like to note that we have one child with hypertonic dehydration as a result of gastroenteritis, who was apparently normal mentally before this illness but subsequently is mentally retarded and has maintained a serum sodium of 155 to 160 mEq. per liter for over a year. Her initial serum sodium was 200 mEq. per liter. In relation to Dr. Forbes's remarks, we did not see much disturbance of the central nervous system unless the serum sodium exceeded 160 to 165 mEq. per liter.

Finally, I might add that this reminds me of a recent Letter to the Editor in one of the Cleveland papers. The writer was concerned about the proposed fluoridation of the water; he stated that he was opposed to this because "there are too many chemicals in the body already."

Metabolic Observations in Newborn Infants of Diabetic Mothers. Dr. C. D. Cook (by invitation), Boston, D. O'Brien, M.B. (by invitation), London, Dr. J. D. L. Hansen, Capetown, South Africa, Dr. M. Beem (by invitation), Chicago, and Dr. C. A. Smith, Boston.

Many observers have noted that diabetic mothers' infants are both heavier and longer than normal infants. Clinically it has been felt that this increased weight was at least in part due to a relative increase in the amount of body water present at birth. Since unusual body composition of a newborn infant may be revealed by the pattern of metabolic adjustments during the first few days of life, the urinary outputs of water, Na, K, Cl, and N of the 19 diabetic mothers' infants were measured during the first three postnatal days. These results were compared with similar determinations on premature and term infants of normal mothers (previously reported).

When the comparisons were made in accordance with body mass, the Na, K, and Cl excretions of the diabetic mothers' infants were significantly greater than those of the control infants of comparable birth weight.

On the other hand, when the electrolyte excretions of diabetic mothers' infants were compared with those of the same control infants on the basis of gestational age, there was no significant difference between the two groups as a whole. A few infants of diabetic mothers did show outputs of Na, K, and Cl which were excessive even for their gestational ages.

Serum Cl values were followed in 10 of the diabetic mothers' infants, but no significant or consistent changes were noted, and no differences were found between these values and those for control infants.

The N excertions were proportionately larger in the smaller and more premature infants of both groups, but no differences were apparent between the diabetic mothers' infants and normal infants on either basis of comparison.

Urine volume and weight losses were definitely larger for the diabetic mothers' infants than for normal infants of comparable weight groups similarly cared for in humidified air and without oral intake.

Thus diabetic mothers' infants behave as a group in respect to electrolyte and water excretion, unlike normal infants of comparable size but like infants of comparable gestational age. If sodium and chloride excretions following birth are used as indices of edema present at birth, it would appear that diabetic mothers' infants have approximately the amount of edema per kilogram that one would expect from their gestational age, though definitely more than normal infants of the same weight.

However, the individual variations within the group of diabetic mothers' infants were considerable, and there was no constant relationship between excessive birth weight and water or electrolyte excretions during the first three postnatal days. Hence it appears probable that other factors in addition to excessive water retention may well acount for at least part of the excess weight of these infants.

DISCUSSION

Dr. Clement A. Smith, Boston: These data have been very tantalizing, because no clear pattern emerges from them. Perhaps this may be because they were obtained from infants who, on the whole, were less abnormal than those often born to diabetic mothers. Infants who were extremely edematous in appearance and who were having some evidence of respiratory distress were not considered proper subjects for our urine collection.

If one had a series composed only of the most obviously edematous infants, possibly there might emerge some clearer relationship between excess birth weight, excess weight loss, and excess urine volume, to indicate that the increased birth weight was accounted for by an extra amount of water in the tissues.

We are entirely aware of the fact that it may be incorrect to measure the composition of the infant by what he is prepared to discard after birth. On the other hand, because of the precarious status of these infants, it is obviously difficult to utilize a more direct approach.

Dr. Walter Heymann, Cleveland: As we all know, macrosomic babies are not born to all diabetic mothers, but to many. Among a series of 10 multiple pregnancies in diabetic women, we found that if the diabetic mother once had a macrosomic baby, the following pregnancies were likely to produce macrosomic babies again.

The reverse was also true: if the newborn infants were not of heavy weights, the following pregnancies were not likely to produce overweight babies again.

There were 2 exceptions in a series of 10 multiple pregnancies in diabetic mothers in which the pattern was irregular. In that this observation may be of value to the obstetrician in evaluating the difficulty of the next pregnancy, I would be interested to hear whether Dr. Cook had similar experiences.

Dr. Dane G. Prugh, Boston: Recently, I came across an abstract of an article which dealt with this same area, and which reported that the babies of diabetic fathers also were above the average in weight at the time of birth. This occurred in instances in which the mothers were not diabetic. I don't recall the details of the study or whether it has been confirmed by later observation, but I am interested to know if Dr. Cook has any comments on it.

Dr. Lytt Gardiner, Syracuse, N. Y.: I should like to ask Dr. Cook if he has been able to make any observations on the histology or the histochemistry of the adrenal cortex in diabetic mothers' babies.

Secondly, I should like to comment on what is impressing us: the striking diversity of the mammalian placenta from the endocrine point of view. This organ apparently takes onto itself a remarkable number of endocrine functions during the latter part of fetal life, and, very likely, is autonomously regulating water and salt transport in and out of the fetal circulation. I wonder

if your colleague, Dr. Claude A. Villee, at the Boston Lying-in Hospital, has made observations on enzymatic lesions in the placentas of diabetic mothers. One might suspect that it would be at this site that we would find the key to this interesting problem.

Dr. C. D. Cook, Boston: If Dr. Gellis is here, I should like to refer Dr. Heymann's question as to whether or not diabetic mothers have consistently overweight infants to him. It is my impression from our small series that our data agree with those of Dr. Heymann.

In reply to Dr. Prugh's question, we have no original data concerning the offspring of diabetic fathers.

We have not studied the histochemistry of the adrenals of diabetic mothers' infants, and hence cannot answer Dr. Gardiner's question.

I feel that one comment, perhaps, is worth while, and that is in regard to some of the work from Dr. C. H. Best's laboratory, showing that insulin possibly has a growth-promoting effect in addition to its effect on carbohydrate metabolism. Further work along this line may provide some information as to why many of the infants of diabetic mothers are large in size.

Dr. Sydney Gellis, Boston: In our series of 600 infants of diabetic mothers, we noted that some mothers tend to produce increasingly edematous and large babies with subsequent pregnancies. However, in the great majority of these mothers there appears to be no relationship between the size of the baby and edema and the order of pregnancy.

Sites of Action of Parathyroid Hormone—Studies on Pseudohypoparathyroidism. Dr. Philip L. Calcagno (by invitation) and Dr. Charles U. Lowe (by invitation), Buffalo.

The cause of the phosphaturia and hypophosphatemia which ensue following injection of parathyroid extract is not clearly defined. Two separate effects have been investigated: one a renal response, the other a bone effect. The renal response has been shown by some workers to be primarily a reduction of tubular reabsorption of phosphorus. Others have demonstrated an increase in glomerular filtration rate (GFR) and suggested that the phosphaturia is secondary to this increased phosphate load and largely independent of an alteration in tubular reabsorption of phosphorus.

Since patients with pseudohypoparathyroidism are known to develop no hyperphosphaturia following the intravenous injection of parathyroid extract, it seemed appropriate to investigate the effects in such patients of this hormone on GFR and serum phosphorus concentration.

GFR was measured by insulin clearance, and the effect of subsequent parathyroid extract injection upon this function and upon phosphate excretion was determined. Based upon these measurements, phosphate reabsorption could be calculated.

In the normal subject the following observations were made: The intravenous administration of 200 units of parathyroid extract resulted in an increase in GFR of 35% and a threefold and tenfold increase in phosphorus excretion. In striking contrast, however, were the results obtained from the same subject when a similar dose of parathyroid extract was injected intramuscularly. The GFR did not change, but the phosphorus excretion, nevertheless, rose threefold.

Similar studies were then performed on a patient with pseudohypoparathyroidism. It was observed that not only was there no significant effect of parathyroid extract on phosphaturia, but neither was there a change in GFR or tubular reabsorption of phosphorus regardless of route of administration of parathyroid extract.

The administration of parathyroid extract by both routes of administration resulted in a fall in serum phosphorus and a rise in serum calcium in the normal patient. In contrast, however, in the patient with pseudohypoparathyroidism, after administration of parathyroid extract, both intravenously and intramuscularly, there was a rise in serum phosphorus and serum calcium concentration.

These data suggest the following conclusions:

1. Depending upon route of administration, parathyroid extract exhibits effects on GFR and/or tubular reabsorption of phosphorus.

2. While the intravenous administration of parathyroid extract to a normal person may cause a rise in GFR, the phosphaturia can occur independently of such an increase in GFR.

3. Patients with pseudohypoparathyroidism exhibit a previously undescribed abnormality, i. e., a failure to achieve an increase in GFR following administration of parathyroid extract.

4. It appears that part of the effect of parathyroid extract must be due to an effect upon bone, since in patients without renal response, there is, nevertheless, an increase in serum calcium and phosphorus.

DISCUSSION

DR. WALLACE W. MCCRORY, Philadelphia: I wish to congratulate the authors for a very interesting study. I should like to make just a few comments. The first one would be that, in the introduction, the authors stated that the work of three of these previous investigators was unclear. For this I would substitute "inconsistent and coldly contradictory." With that beginning, I feel that I can make my few comments.

As many of you know, at New York I had the opportunity with Dr. Florman and Dr. Barnett to give intravenous parathyroid extract to about 15 babies. Try as we did, we were unable to see any consistent effect of intravenous parathyroid hormone on glomerular filtration rates in these infants. I believe that this is of some importance in the sense that the nature of how parathyroid hormone works is confused enough without getting into an argument as to whether or not it has a consistently reproducible effect on glomerular filtration rates in normal people.

We recently had an opportunity to do what we thought was presented here. Our patients ceased to have pseudohypoparathyroidism when we gave them a potent form of the extract.

We got word of a death that had been reported as a result of the injection of intravenous parathyroid hormone. Consequently, we gave intramuscular injections to the hypoparathyroids, with exactly the results we have seen here—marked increase in phosphaturia and no change in glomerular filtration rates.

I would be interested in the comments the author might have to make as to whether he believes that the effect on glomerular filtration rate is a specific effect of the hormone or a foreign protein effect.

DR. HAROLD HARRISON, Baltimore: There is a very small but highly vociferous group that seems to be interested in the effect of parathyroid hormone on renal excretion of phosphate. We got into it, perhaps to our regret, some years ago and reported what we thought were clear-cut evidences of reduction of tubular reabsorption of phosphorus as a result of intramuscular injection of the parathyroid extract. Subsequently, other workers extended the observations. Many of them gave the parathyroid hormone intravenously, and the beginnings of a certain amount of conflict developed.

The difference in the route of administration is highly important. Perhaps more important than that is the question of the purity of the parathyroid extract. I should like to ask Dr. Calcagno whether he has considered the possibility of two types of parathyroid hormones. That question has come up repeatedly in the past. I noticed that recently a group in Boston assayed parathyroid extract in two ways, using what they called a calcemic response and the phosphaturic response. Commercial parathyroid extract gives little phosphaturic response, but is potent with respect to the calcemic response.

In their hands, a freshly prepared parathyroid extract made according to the original method had a marked phosphaturic effect, so that the ratio of calcemic to phosphaturic effects was quite different when commercial extract and freshly prepared extract were compared. That would suggest that there are two parathyroid hormones or, if there is one parathyroid hormone, that one of its effects is lost on deterioration of the protein material.

Would it not be possible that in the patients with so-called pseudohypoparathyroidism the administration of a much more potent freshly prepared parathyroid extract might produce an effect upon renal tubular reabsorption of phosphate?

I believe that this is an extremely nice opportunity to utilize a patient with an abnormal response to parathyroid hormone, in an attempt to solve what still is—and I agree with Dr. McCrory on this point—a highly confused subject.

DR. HENRY L. BARNETT, New York: I feel that what both Dr. McCrory and Dr. Harrison were saying is that anyone who has worked in this field gets very nervous when anybody starts to talk about it, and I admire the courage of the authors for entering into it.

I should like to ask two questions: In relation to the so-called acquired resistance to the effects of parathyroid extract, I should like to ask whether the patients with pseudohypoparathyroidism had had parathyroid extract (Parathormone) in the past; and, secondly, whether the authors had the opportunity of making repeated observations in the same patient or normal subject to see whether any change in response to parathyroid extract developed.

DR. ROBERT KLEIN, Pittsburgh: I should like to say just one word in defense of Dr. Calcagno. I don't believe that the results have been that inconsistent with our intravenous administration. I believe that we felt that the major effect was that on the tubular reabsorption and that the difference between our results and Dr. McCrory's may well have been a question of protein, or what have you, because we used much larger doses.

Incidentally, when the period right after the administration of intravenous parathyroid hormone was short enough, there was an initial depression of glomerular filtration rate, which may have been spurious but seemed to have been consistent. I believe that probably the differences can be explained on a dosage phenomenon.

DR. ALLAN M. BUTLER, Boston: I should like to make two comments. First, I should like to comment on the nicety of the experiments conducted and the clarity with which the data were presented; second, I should like to remark that there is much more agreement in this field than has been indicated by some of the comments of the discussers.

Some of the disagreement is pointed out by the possible difference in intravenous and intramuscular injection, so nicely shown by the presented paper. Also, some of the disagreement in results is undoubtedly due to the lack of uniformity of the commercial extracts that have been used. But I should like to stress that there is good agreement, I think, on the renal and nonrenal effects, so nicely demonstrated in the presented paper, on the effect of extracts on patients with pseudohypoparathyroidism.

I wish that Dr. Crawford or Dr. Talbot were here, but they had to be in Atlantic City. They could more accurately than I state the agreement between their results and the results reported today.

DR. PHILIP L. CALCAGNO, Buffalo: First I should like to thank all of the discussants.

In regard to Dr. McCrory's question as to his not being able to obtain consistent effects upon glomerular filtration rate when the extract was given intravenously, I should like to say that I am deeply sorry. Our information is very consistent and clear.

Second, as to whether or not the effect upon glomerular filtration rate is a protein effect or a specific effect, we don't know the answer to that.

From the literature, one is impressed with the indication that perhaps it may be a protein effect.

In answer to Dr. Harrison's question regarding the possibilty of several types of parathyroid hormones, I must say that we have done no work to answer this question. I will say that references exist in the literature to indicate that there are many effects of parathyroid extract: on glomerular filtration rate, on blood pressure in rats, a calcium effect, a phosphorus effect, and even an effect on growth.

Concerning Dr. Barnett's two questions, first, whether the patient had received parathyroid extract previously, the answer is no, because the patient had not been known as a patient of pseudohypoparathyroidism.

Second, the repeated observations were done four times during a two-year period on this patient to make absolutely sure that the results were consistent. The response in each instance was the same.

Concerning Dr. Klein's comments, I should like to thank him again for coming to our defense, but I should like to say also that the consistency of his data and our data should be the real defense.

Respiratory Alkalosis—A Frequent Phenomenon Observed in Newborn Infants. DR. H. S. REARDON, Haverford, Pa., M. L. BAUMANN, B.S., and DR. E. J. HADDAD, Philadelphia.

The purpose of this report is to present a new concept of respiratory physiology in the early neonatal period, based on studies which were designed to evaluate the chemical factors involved in the respiratory control of acid-base balance.

With temporal artery blood, serial determinations were made at 1, 4, 24, 48, 72, and 96 hours of life on 29 well, full-term, fasting, noncrying infants. Umbilical artery blood was obtained from 16 of these infants. Analyses were made for plasma pH, CO_2 content, O_2 content, and capacity and hematocrit. The CO_2 gas tension (pCO_2) and O_2 saturation were calculated.

The results reveal that the pCO_2, which is slightly elevated (49 mm. Hg) in the umbilical artery blood at birth, decreases rapidly, so that within one hour after birth the pCO_2 of temporal artery blood is in the normal adult range (38 mm. Hg). The pCO_2 continues to decrease during the first day to subnormal values (average: 33 mm. Hg) and remains below normal until approximately the fourth day of age, when it again approaches the normal adult range. The rapid fall in pCO_2 from 49 to 33 mm. Hg within the first day of life is a good indication that the ventilatory ability of the newborn lung is adequate very shortly after birth.

The decrease in pCO_2 coincides with a rise in pH from a mean of 7.30 to 7.38 at 24 hours of age. Thereafter the pH remains relatively constant. At one hour of age, the mean pH value of 7.30 indicates an acidosis. However, from 24 hours through 72 hours of age, the pH is in the adult normal range, but both the CO_2 content and pCO_2 are slightly low. The lowered CO_2 content (20.2 mEq. per liter) indicates a decrease in alkali reserve or metabolic acidosis. The decreased pCO_2 (33 mm. Hg) indicates hyperventilation or respiratory alkalosis. The changes in CO_2 content and pCO_2 may have been initiated independently of each other, or the decrease in pCO_2 may be compensatory for the decrease in base bicarbonate. Regardless, these changes are those of a mixed disturbance of the acid-base balance, i. e., metabolic acidosis and respiratory alkalosis.

The O_2 saturation studies reveal no evidence of anoxia after four hours of life in the majority of infants. The average O_2 saturation value is 93% at 4 hours of life and 95% or above after 24 hours.

These data reveal that sometime after 4 hours of life and by 24 hours of life respiratory activity continues with a partial pressure of CO_2 gas, below a level considered necessary for driving the respiratory centers. It is apparent that the respiratory centers are not being driven by anoxia during this same period, since the O_2 saturation of the blood is very close to or at the adult normal range. Although conclusive evidence is not presented in this study, it is suggested that pH has an important role in the maintenance of adequate ventilation in the first few days of life.

DISCUSSION

DR. SOLOMON A. KAPLAN, Brooklyn: I did not follow Dr. Reardon's reasoning completely and wonder if she would elaborate a little on why she concludes that respiratory alkalosis was present. As I remember the data which she presented, the low pCO_2 which developed was accompanied by a pH which was below the normal range and by a low CO_2 content.

The data seemed to indicate a metabolic acidosis (after the initial respiratory acidosis), in which the pCO_2 was lowered in an attempt to restore the pH to normal. It was not clear to me why the low pCO_2 was interpreted as evidence of primary respiratory alkalosis, since the pH was always on the acid side of normal.

DR. JOHN A. ANDERSON, San Francisco: Observations on the arterial capillary oxygen in the hand as compared with that in the foot, made by Ulster, at Stanford University, the last year or so, indicate differences which suggest the possibility of the physiologic reverse ductus situation and that these changes back to oxygen saturations in content in both arms and legs occur in about the same sequence that has been presented by Dr. Reardon.

I wonder if observations on the oxygen in the foot, as well as the CO_2 and pCO_2 in the foot arterial blood, were made to correlate with the observations in the temporal artery.

DR. HELEN S. REARDON, Haverford, Pa.: In reference to Dr. Kaplan's question, I suppose that it is partly a matter of semantics. What we have tried to demonstrate was that shortly after birth the blood chemical findings of an uncompensated metabolic acidosis (low CO_2 content, low pH, and normal pCO_2) are rapidly changed to a compensated metabolic acidosis by a decrease in pCO_2 and an increase of pH to the normal range. A decrease in pCO_2 indicates hyperventilation or respiratory alkalosis. Thus the chemical findings of a decreased pCO_2 with a normal pH may be called compensated respiratory alkalosis, just as the chemical findings of a decreased CO_2 content and normal pH are usually designated as compensated metabolic

acidosis. The important point is that newborn infants have the blood chemical findings of hyperventilation for a few days after birth in addition to a low CO_2 content of the blood. This may be designated as a mixed disturbance of the acid-base equilibrium.

Dr. Singer and Dr. Hastings, I believe, prefer to discuss these mixed disturbances in terms of buffer base and pCO_2 deficit or excess and have pointed out various interrelationships in certain disease entities.

In reference to the other question of comparing the chemical findings of the blood obtained from the temporal artery with the chemical findings of the blood obtained from the leg artery, we have done no such studies. If Dr. Graham is in the meeting, I wish that he would comment on his chemical studies of capillary blood obtained from the heels of babies shortly after birth and throughout the first day of life.

DR. BRUCE D. GRAHAM, Ann Arbor, Mich.: We have done at Ann Arbor a few studies of this type. We did capillary sampling from the heel of infants 4, 8, 12, and 24 hours of age. These results correlated well with arterial blood studies.

Dr. Reardon has done a nice piece of work here, that complements our work, the results of which have recently been published. The point we were trying to make is that we believe that hypoxia is the driving force of early maintenance of control in these infants.

Mineral Balance Changes Induced by Pyridoxine in Infant Receiving Convulsigenic Feeding Mixture. DR. ARILD E. HANSEN, HILDA F. WIESE, Ph.D., DR. DORIS J. D. ADAM, (by invitation), DR. DAN R. BUSSEY, (by invitation), and DR. A. G. WORSHAM, (by invitation), Galveston, Texas.

One of the most phenomenal happenings in the history of infant feeding was the relatively recent observation that convulsions occurred in certain infants receiving a well-known and long-accepted type of milk mixture, which was designed to emulate human breast milk. Why only certain infants maintained on the particular preparation developed grand and petit mal seizures seemed to demand explanation. In animal studies, it has been long recognized that vitamin B_6 deficiency is associated with convulsive seizures, which are relieved by the administration of pyridoxine. The mechanism involved is obscure. A possible relationship between the occurrence of convulsions and the minerals in the diet has been demonstrated by McQuarrie, Hansen, and Ziegler (1941) in studying the influence of vasopressin injection (Pitressin) on seizures in idiopathic hypoparathyroidism. The presence in our hospital of a 4-month-old infant suffering from convulsive seizures when maintained on the above milk preparation afforded the opportunity to study the effect of pyridoxine on the mineral balance. During a four-day interval in which six convulsions were observed, the nitrogen retention was 61.8 mg. per kilogram per day. The retention of the following minerals in milliequivalents per kilogram body weight per day was phosphorus, +0.98; chloride, +0.42; sodium, —1.15; potassium, +3.2; calcium, +1.11; magnesium, +0.14. Pyridoxine (10 mg.) was given orally for six days, which event coincided with a dramatic change in the child's disposition and the complete cessation of convulsive seizures. The average daily consumption of the milk preparation increased by 37%, but the nitrogen retention was 159 mg. per kilogram per day, a two-and-one-half-fold increase. The relationship between vitamin B_6 and protein metabolism is well known, but any specific effect of intermediate nitrogenous compounds on convulsive seizures has not been recognized. The retention of minerals was also increased during this period. The following values expressed in milliequivalents per kilogram per day were found: phosphorus, +1.60; chloride, +1.52; sodium, —0.10; potassium, +7.1; calcium, +1.98; magnesium, +0.32. In the six-day period following the discontinuation of pyridoxine, additional increases occurred in retentions of calcium and magnesium, particularly the latter. The child's condition remained excellent. In a subsequent four-day period, with the infant on the same type of diet, the retention of phosphorus, calcium, and magnesium decreased markedly, the values approaching those of the convulsive period. The significance of the ratio of various minerals to neuromuscular irritability, though not understood, has been believed to be important. Detailed consideration was given to the urinary excretion during the four periods of observation. Outstanding was the marked reduction in the urinary output of magnesium compared with that of calcium. The urinary excretion of magnesium for the four periods was 0.78, 0.54, 0.11, and 0.32 mEq. per day, respectively, and for calcium the values were 0.25, 0.57, 0.40, and 0.40 mEq., respectively. It is suggested that the metabolism of

certain minerals may be related to the convulsive mechanism produced when infants are maintained on the milk mixture in question. Experimental animals on pyridoxine-deficient diets are being studied to test this hypothesis.

DISCUSSION

DR. CHARLES D. MAY, Iowa City: Many of us have been interested in this extraordinary occurrence of pyridoxine deficiency in infants fed milk products. I wonder, however, if the sort of data which Dr. Hansen is presenting allows us to gain any insight into the pathogenesis of this disorder. If any essential nutrient is withdrawn from the diet, one of the inevitable consequences in anorexia and loss of weight. With the restoration of this essential nutrient, one finds increased appetite and gain in weight, and under such circumstances positive balance of many items would be inevitable.

Dr. Hansen showed in his slides that the milk intake in his babies increased by about 40%. Therefore, the retentions do not necessarily reflect the specific adequacy or inadequacy of the previous diet but rather the retentions in an infant heretofore underfed.

We noticed that the plasma concentrations of calcium and phosphorus were normal and could not be related to the seizures. Furthermore, upon continuation of this diet, with the addition of a modest amount of pyridoxine, the convulsions ceased instantaneously. The hypothesis that other factors may be involved in the seizures can be raised; these factors, in turn, depend upon the deficiency of pyridoxine. We should not be led to assume that the mineral content of human milk is inadequate or that those amounts supplied by products which contain similar amounts are inadequate. Rather, we should focus our attention on the role of pyridoxine in metabolism.

DR. ALLAN M. BUTLER, Boston: My remarks are directed to clarification, lest we are misled by misunderstanding. For this purpose I should like to supplement what Dr. May has said.

Dr. Hansen's paper nicely calls attention to the possibility that an intracellular defect due to pyridoxine deficiency might be responsible for the convulsions of these babies. It will not, I trust, lead any of us to believe that breast milk isn't a proper nutrient. I take it that there is nothing in the paper to suggest that you can protect children from convulsions by giving a higher electrolyte diet than that provided by breast milk or that the low protein content of breast milk is perhaps the factor that may predispose to convulsions.

Then to keep us all from being apprehensive about the milks that we may be prescribing for our infants, we ought to say very frankly that the product that seems to have been deficient in pyridoxine was a lot of S.M.A., produced following a modification in preparation procedures. Whether it was overheating or the effect of resin adsorption we do not know, but whatever the cause, the preparation procedure has been corrected.

This unfortunate accident has fortunately provided quite a lot of new information about pyridoxine deficiency. Perhaps some day some wise biochemist will be able to show us just where pyridoxine is essential in cellular and central nervous system metabolism. Maybe it will be shown to have something to do with magnesium, thus correlating the study reported with the convulsions observed in these youngsters.

DR. CHARLES D. MAY, Iowa City: Will you pardon me for rising again, but as long as the discussion has taken a turn toward the whole question of seizures, I should like to point out that there was a conference in Chicago last summer under the auspices of the American Medical Association, which I had the privilege of attending. There were assembled some of the most outstanding authorities in the country on pyridoxine and its deficiency. No one was able to point to any other explanation for the seizures than the simple deficiency of pyridoxine. Dr. Butler has pointed out that this resulted from a mere accident of autoclaving at a higher temperature in an effort to establish sterility in the product.

If one were to condemn the product on this basis, one might as well condemn pasteurization of milk in general because vitamin C is destroyed in the process. This event represents another advance in our knowledge of the things we do in processing but does not represent anything which leads us to have any unfavorable attitude toward attempts to process foods satisfactorily.

DR. ARILD E. HANSEN, Galveston, Texas: It sounds as though I really should say nothing. I am sure everyone is getting hungry, and we have a certain degree of "pyridoxine deficiency" at the moment.

I am delighted to have it brought out that in the presence of one dietary deficiency there may be associated other types of deficiency with various metabolic features resulting.

In the first place, I assumed that everyone here knew the name of the product in question. I also assumed that everyone was aware that only in the liquid form of the preparation, not the powder, had convulsions developed in infants. I also assumed that everyone was aware of the factor of heat in relationship to destroying the vitamin. In fact, it is reported that vitamin B_6 is the most readily destroyable of all the vitamins used in infant feeding.

I do not feel that we should be above the point of seeking some of the fundamental factors which may be concerned with the production of spasms in infants. I am surprised, really, to find that the leaders of pediatricians seem to have overlooked a significant point in the matter of convulsive seizures in infants. After all, one of the most important problems we have in pediatrics is that of convulsions. This report simply has been an attempt to show that effort has been devoted to try to begin to understand one phase of the problem.

Evaluation of Psychological Effects of Conditioning Device in the Treatment of Enuresis. Dr. F. C. Behrle (by invitation), Miriam Tate Elkin, Ph.D. (by invitation), and Dr. Paul C. Laybourne, Kansas City, Kan.

Favorable reports on the treatment of enuresis using a conditioning device have appeared sporadically for the past 50 years. Despite the very encouraging results of these reports, many phsicians have been reluctant to approve the use of such a device for fear of serious emotional disturbances resulting from what has been called "symptomatic" treatment. This study was undertaken to evaluate this point.

Twenty subjects ranging in age from 5 to 14 years were selected for investigation. Children included in the study met the following criteria: (1) average intelligence or better, (2) 5 years old or above, (3) absence of organic disease involving the central nervous or urogenital systems, (4) absence of daytime wetting, (5) night wetting at least every other night, and (6) willingness to cooperate. No attempt was made to specifically include or exclude children with obvious emotional disturbances.

A history concerning the behavior of the child was obtained from the mother, and a complete battery of psychological tests was administered to each child before employing the conditioning device in the home. The psychological tests were repeated approximately six months after night wetting stopped. The mother was questioned periodically concerning behavior changes in the child both during and after treatment.

The findings in this study were as follows:

1. A great variation existed in the extent of emotional disturbance in the group.

2. Children without severe emotional disturbances appeared to suffer no undesirable effects as a result of this type of treatment.

3. Although the seriously emotionally disturbed children responded very well in respect to enuresis, they all remained seriously disturbed after treatment, and in two cases there was an increase in the severity of the disturbance.

4. Seventy-five per cent of the cases were either completely cured or greatly benefited in respect to their enuresis.

The importance of the manner in which this device was used in this study will be discussed in relation to untoward behavior arising while therapy was in progress.

DISCUSSION

Dr. Milton J. E. Senn, New Haven, Conn.: I am not sure that I understand whether the investigators recommend this form of treatment or not. Certainly, I assume, they realize the opportunities for exploitation of their results by the manufacturer of this instrument. I hope then that they can answer whether they recommend this form of treatment unqualifiedly or with qualifications.

Dr. Arthur H. Parmelee Jr., Los Angeles: Dr. Murray Kahane did a similar study at the University of California Medical Department, Los Angeles, as part of a doctor's thesis. He had about 46 patients, 23 of whom were given this same treatment, using the same conditioning device, and another 23 who were not given this treatment. In a six-month follow-up, about

50% of his patients who were initially treated with the conditioning device reverted and were bed-wetting again, so that he considered that he had a 50% cure rate, if you want to call it that. In his untreated control group, in the six-month follow-up period, he also had a 50% cure rate. This certainly cast some doubt on the effectiveness of the conditioning device. One must state at this point that he did give those children in the control group two discussion periods, in which he reassured and encouraged them.

He also did psychological projective tests on the two groups mentioned and on another group of children who were not bed-wetters and found no major difference in emotional problems between the children who were enuretic and those who were not enuretic.

In other instances, the study was quite similar to this one.

DR. ANDREW HUNT, Flemington, N. J.: I believe that any of us who are at a pediatric level treat any enuretic, regardless of what method we use—whether we use no medication, or whether we use diphenhydramine (Benadryl) or belladonna. One thing we know is that the child who wants to get some help is the one that can get it and has a good prognosis.

The second thing that we certainly know is that, regardless of what theory of enuresis is employed, when the parents are able to somehow turn the responsibility of keeping dry over to the child, there is an excellent chance for a cure.

Now Dr. Behrle did both of these things in this situation. He selected his cases in such a way that these were children who wanted to get better and who were able to take over some responsibility. And secondly, he did an extremely wise thing in talking with these children, so that they would assume some of this responsibility themselves. This was extremely good treatment, but as a method of evaluating the effect of the machine, you throw in two variables, which is against the experimental technique, as I know it.

I should like to know what sort of controls were run in this kind of experiment.

DR. F. C. BEHRLE, Kansas City, Kan.: In answer to Dr. Senn, I would say that we are neither recommending nor disapproving the use of this machine. Our study was aimed primarily at evaluating the psychological effect of its use. The results indicated that in the group studied there were no serious psychological effects acompanying its use. Whether or not this method of treatment is more effective than any other cannot be stated from this study. Our feeling is that if this treatment is going to be used, a number of factors must be taken into consideration, including the child's willingness to cooperate, the severity of any existing emotional disturbances, and the manner in which he reacts to the machine. I personally would not use this method on a seriously disturbed child without first obtaining the benefits of psychotherapy.

This study did not attempt to distinguish between the conditioning effect and the suggestive effect of the device. That there was a definite suggestive effect was very obvious throughout the study. Some of the children who had wet seven nights out of seven, month after month, would become dry when they learned that I would soon be out with the machine—even before the machine was placed on the bed.

Further Observations on Familial Dysautonomia. DR. CONRAD M. RILEY (by invitation), DR. ALFRED M. FREEDMAN (by invitation), and DR. WILLIAM S. LANGFORD, New York.

During the past year, a team consisting of a pediatrician, a neurologist, a psychiatrist, and related specialists has been studying familial dysautonomia. This is a preliminary report which discusses factors not previously emphasized.

Items suggesting a genetic origin have been gleaned from knowledge of 47 cases: (1) all unquestionable cases Jewish; (2) incidence of 25 to 30% in siblings of index cases; (3) occurrence in 2 sets of first cousins; (4) consanguinity in 3 sets of parents. Also, there has been a case reported of a father of nine apparently normal children with his first wife and three affected children with his second.

Twenty-seven patients measured showed an average deviation below mean height and weight greater than could be expected by chance alone, and no patient was significantly above the mean. Postural hypotension of varying degree has been demonstrated in the 15 cases examined.

Neurological examination showed abnormalities in all cases, but only diminished tear production was consistent. Skin blotching, hyporeflexia, absent corneal reflexes, and scoliosis were fairly common. Abnormal use of speech musculature was present in all 12 cases studied. Seven had serious problems of intelligibility despite average language organization.

Twelve patients were tested psychologically. The younger patients (3 to 7 years of age) scored in the average range with regard to "spatial pattern organization" and "body image," whereas the older (9 to 13 years) scored below average. In contrast, abstract thinking as tested by "verbal concept finding" showed that the older children scored higher than the younger and well within the average range.

Behavioral disturbances in the patients constitute a major problem. A vicious cycle is set up, starting with the autonomic homeostatic problems secondary to the postulated central nervous system derangement. The resultant overreaction to emotional stimuli frightens and stimulates guilt in the parents, so they are easy objects for manipulation by the children. This deprives the children of the firm support they seem to need, increasing their insecurity and anxiety. This heightens the autonomic homeostatic problems, perpetuating the cycle.

Despite observed similarities to both schizophrenic and brain-damaged children, the child with dysautonomia stands out as a distinct entity.

The only new useful form of treatment so far tested has been a phenothiazine derivative (Chlorpromazine; Smith, Kline & French's Compound 2601-A). This has proved effective in helping to control the vomiting, which may be the most distressing manifestation.

A proposed method of management is the establishment of a rigid schedule by the doctor, removing responsibility from the parents. Hopefully, as the external environment is made more secure for the child, the vicious cycle is broken, and the lack of autonomic homeostasis becomes less handicapping.

Suggestions are given for further studies.

DISCUSSION

DR. SAMUEL KARELITZ, New York: I am sure that if Dr. Riley had sufficient time, he would have gone into many other details of this curious condition. Dr. Ralph Moloshok and Dr. Richard Reuben have recently pointed out that infants with this condition behave in a characteristic pattern. The infants do poorly from the very beginning, are thought to have colic, eat poorly, and gain slowly. These facts were established only in retrospect; that is, it was finally ascertained by history that the children fell into this category, which we in New York call the Riley-Day syndrome.

I have an extraordinary case of this type, which was seen by Dr. Riley. This child had been in a so-called "coma vigil" for about 11 weeks. I had seen this boy once in the second year of life because of recurrent bronchitis, high fevers, and malnutrition. Now he is a little over 4 years and has been known to Dr. Riley for some time. He qualifies for this category of dysautonomia. He has no tears. He has somewhat unsteady blood pressure. He runs extraordinary high temperatures without provocation, and for which no explanation is usually found, and repeatedly has what we believe to be a bronchitic episode, only to recover spontaneously in a day or two. Frequently the entire chest is full of moist rales, and four to eight hours later it is perfectly dry. In the previous six months he has had repeated convulsions, at first brought on by breath holding and more recently without known provocation.

After one such convulsive seizure, about three months ago, accompanied by a hyperthermia of 106 to 107 F., he remained in coma, and he is still in that state. He has been fed by tube except during episodes of vomiting, when he is kept going by intravenous fluid.

As of July 10, 1954, this child is still in the same state of coma vigil. He has never been lucid since the onset of this episode. A pneumoencephalogram reveals moderate dilatation of all ventricles and possibly some atrophy in the frontal lobe areas.

DR. MILTON J. E. SENN, New Haven, Conn.: I belive that it is rare to have papers presented before this society on physiological and pathological phenomena that include the psychological considerations. This being so, I should like to congratulate the authors and investigators of this work. I feel that it is extraordinary that they have been able to integrate the psychologic with the physiologic so well.

DR. CONRAD M. RILEY, New York: Thank you, Dr. Karelitz and Dr. Senn.

This point that Dr. Karelitz brought up about making the diagnosis in early life is an interesting one. Actually, the only times that we have made it with any assurance is when the patient has been a sibling of a known patient. On two such occasions, at least, the child failed

to suck well in the neonatal period. We were unable to elicit any deep tendon reflexes, and as we watched the child grow to the age at which we expected tears, which is about 6 to 8 weeks, these children failed to begin to produce tears with crying.

I believe that actually in a family in which there has been no previous case, it is impossible to be sure of this diagnosis before the first year or a year and half of life, because so many of these things happen with other examples of brain damage. I feel that all one can do, in the early phases, is raise the suspicion.

Dr. Karelitz' patient, who has had some kind of severe brain-damage episode, is unique in my experience. I haven't seen anything else like it, and I am at a loss to understand exactly what happened there.

Death Due to Accidental Poisoning in Young Children. Dr. Katherine Bain, Washington, D. C.

Prompted by Swinscow's article on deaths from accidental poisoning of young children in England and Wales during the decade 1940-1949, a review was made of the United States experience over the same period. Instead of 900 cases, the number expected on the assumption that United States and British experiences are similar, more than 3,600 were found. The United States rate for this period was 3.6 per 100,000 population, more than four times the British rate of 0.87. Reasons why young children in the United States should be in so much greater jeopardy from poisoning than those in Britain were sought through detailed analysis of data from death certificates for the years 1949 and 1950. The interesting phenomenon of male susceptibility to accidental death, true for most categories of childhood accidents, holds for poisoning also. The male-female ratio is 3 : 2. Nonwhite rates in the United States for accidental poisoning are greatly in excess of white rates (three times higher) but are not sufficient to acount for the differences between the two countries.

When the substances causing accidental death by poisoning are examined, some explanation of the high United States incidence is found. The poisonous substances were grouped into broad categories, which indicate in general the circumstances under which they were obtained: (1) drugs, (2) petroleum products, (3) materials intended for external use, (4) noxious foodstuffs, and (5) unclassified. Drugs, especially for white children, are a greater hazard in the United States than in England and Wales, probably because of the higher income and the greater availability of medicines in the home. Acetylsalicylic acid and the barbiturates are the greatest source of danger. Iron, though common in England, is relatively uncommon in the United States.

The petroleum products, especially kerosene, produce more than 100 deaths yearly and are the major factor in increasing the United States rate. Other materials for external use, such as lye, are especially common in the United States. In addition to the usual household poisons, such as furniture polish and permanent-wave solution, some of the newer poisons are appearing, notably chlorophenothane (D.D.T.) and parathion. Lead and arsenic rates are also high.

Twelve Southern states have a rate twice as high as the remainder of the United States. This difference is accounted for largely by the disproportionate number of deaths from petroleum products (kerosene) and corrosives (lye), the Southern rates being four times and six times as high as the rates for the rest of the United States. The pattern of living and the low economic status of the nonwhite population in the South are probably reflected in these figures.

Roughly two-thirds of the deaths from accidental poisoning could be wiped out if acetylsalicylic acid, the barbiturates, kerosene, lye, lead, and arsenic were not available to small children.

DISCUSSION

Dr. Charles Hendee Smith, New Brunswick, N. J.: I should like to say a word about the great danger of flavoring acetylsalicylic acid. Every company vies with every other to put out acetylsalicylic acid for babies. In the first place, they put them out in different strengths, so that when the mother says she is giving baby acetylsalicylic acid, you do not know which she is giving, unless you inspect the bottle.

In the second place, flavored acetylsalicylic acid tastes good, and children eat it. I feel that this Society should go on record in some way against making candy out of drugs.

The other type of poisoning with which I come in contact is petroleum. In the town in which I live there is a university with a faculty housing unit which has kerosene burners. The fuel is

kept in the back yard, with a faucet on the barrel. The faucet to runabouts means water to drink. These faculty children (not underprivileged children) frequently go to the faucet and get a good drink of kerosene. Then we have to wash out their stomachs.

DR. ROLAND B. SCOTT, Washington, D. C.: Aside from the important factual data in this paper, I feel that it is important for another reason, namely, it puts the emphasis on certain environmental factors which explain, at least in part, the greater incidence of certain types of poisonings in different regional and racial groups in our population.

In the pediatric service of our hospital, ingestion of lye and kerosene acounts for about 50% of all cases of accidental poisoning in children.

The state committees mentioned by Dr. Bain may serve a valuable purpose in collecting data which may be germane to determination of responsibility for death in each reported fatality due to accidental poisoning.

Also, I believe that it is interesting to note that many pediatricians now include a word of advice to mothers regarding accident prevention during the well-baby conference visit. It is also encouraging to know that some of the larger cities are now setting up central stations where cases of accidental poisoning can be treated, collected, and classified. Moreover, these centers are equipped to promptly supply valuable information regarding emergency care and antidotes for various poisons to practitioners and resident physicians in other hospitals upon request.

DR. ROBERT J. MCKAY, Burlington, Vt.: Like Dr. Smith, I should like to reassure the Southern members here by saying that in Vermont we have a very high incidence of kerosene poisoning for similar reasons.

I should like to ask Dr. Bain a question which may be applicable to the difference in incidence in Great Britain and the United States and the difference in incidence between white and Negro children. Were your rates figured on the basis of 100,000 total over-all population or on the population in the age groups with which you were dealing? Obviously, this might make a difference and would depend on the relative number of persons in the various age groups here and in England and the number of white and Negro children in this country.

DR. BORDEN S. VEEDER, St. Louis: I am the culprit who said that I thought it was probably 900 deaths, based on Swincow's report. It shows how a theoretical figure on a population basis can be wrong, and I was quite shocked when Dr. Bain wrote me and said that they turned up over 3,600 deaths. A great deal of that incidence, as she pointed out, is due to the hydrocarbons. Some of the things that are included as miscellaneous, such as floor polishes, are hydrocarbons, so this cause is probably higher.

The thing that interests me is the fact that today accidents are the commonest cause of death among children over 1 year of age in the United States.

Thirty-three per cent of Dr. Bain's figures and about 66% of the English-Wales figures are due to the ingestion of drugs. I feel that we, as physicians, and the pharmaceutical houses have a very definite responsibility in this matter. I do not believe that it is one that we can shrug off. I feel that it is up to us in some way or another to insist that these drugs be properly labeled as dangerous if taken in excess quantity.

Take the cases of acetylsalicylic acid poisoning. Dr. Hartmann and I calculated that there are probably 12 cases of acetylsalicylic acid poisoning brought into the hospital for treatment for every death due to the drug. This means that over a thousand cases of acetylsalicylic acid poisonings, severe enough to need medical treatment, due to carelessness and ignorance, occur in the United States every year. I feel that it is very important that we as physicians, and particularly as pediatricians, should take some definite means to try to stop this high frequency of accidental poisoning due to medicaments and which are so often fatal.

DR. RANDOLPH K. BYERS, Boston: There are two points I want to speak about briefly. I have just been looking over the figures for lead poisoning in Children's Hospital, in Boston, and in the last seven years, 1947 through 1954, March 1, we saw 49 cases of lead poisoning, in 6 of which the patients died. Of the remaining children, 10 or 12 are still too young to tell about, but about half of them are defective mentally in one way or another. So that not only is there the question of death from this cause but there is also the question of mental incapacity, which is even more serious, i. e., more numerous in this instance.

As to the reason that this poisoning is commoner in the North than in the South, I should like to hazard one guess, which is worth looking into. The very large majority of our children with lead poisoning come from the poor housing portions of Boston, which were built in the 1870's and 1880's. At that time, lead chromate, either in the form of chrome green or chrome yellow, was a very common pigment used on the interior trim of the buildings, and a very high proportion of our patients have gotten their lead poisoning from this pigment, which, I believe, was not used in the building of industrial developmental housing later than about 1900. I believe that that may have some bearing on the difference between the North and the South in this regard. In addition, alertness of doctors in suspecting the diagnosis may be important.

Finally, in relation to phenobarbital, I just left a little boy of 5 years, who had a convulsion Sunday, a week ago, and received 13 grains (0.8 gm.) of various barbiturates intramuscularly and rectally in 24 hours. He pulled through, but he is moderately decerebrate now.

DR. KATHERINE BAIN, Washington, D. C.: I am afraid that I cannot answer some of these questions. I quite agree, Dr. Smith, that flavored acetylsalicylic acid is undesirable. I am always impressed with the fact that babies will eat anything, whether it tastes good or not. Certainly kerosene doesn't taste good, but children drink it.

Dr. McKay made a very interesting observation on the incidence of kerosene poisoning on college campuses where married students are living in temporary housing. This was new to me. He asked also about the basis for computing rates. These are age-specific rates, the number of cases being related to the number of children in the particular age bracket.

Dr. Davidson asked me why, when the British have free medicine, we have more deaths. I don't know.

The comments on the difference between the North and South on the incidence of lead poisoning interested me, because in the West, where most of the construction is newer than in the East, lead poisoning is also very very rare. I found only two cases in this material from the West Coast—one in California and one in Washington.

Mucoviscidosis: An Evaluation of Continuous and Prolonged Antibiotic Therapy.
DR. H. SHWACHMAN (by invitation), P. CATZEL, M.B.B.CH., D.C.H. (by invitation), DR. P. R PATTERSON (by invitation), and DR. M. STOPPELMAN (by invitation), Boston.

A presentation will be made of a large group of patients (over 120) treated with continuous broad-spectrum antibiotics. Special emphasis is placed on the pulmonary aspects of the disease, because the prognosis in general is dependent on the severity and rate of progression of pulmonary involvement. The patients were selected on the basis of having at least one full year of continuous therapy with chlortetracycline (Aureomycin) or oxytetracycline (Terramycin).

This report will be in the nature of a progress report inasmuch as five and one-half years have elapsed since chlortetracycline was first used in the treatment of mucoviscidosis. The analysis of clinical data will be presented with emphasis on (1) nutritional status and (2) respiratory tract status, i. e., with analysis of symptoms—cough, dyspnea, exercise, tolerance, clubbing, etc. The side-effects of prolonged chlortetracycline and oxytetracycline therapy will be mentioned. The findings of serial roentgenograms of the chest will be presented. In 99 cases so far analyzed, 56 showed progressive changes (33 alive and 23 dead); 24 have shown no change during the period of antibiotic therapy, while 5 patients actually showed improvement. Fourteen patients have had no or minimal nonspecific changes in the lungs during the period of observation. Brief presentation of bacteriological studies as to the effect of broad spectrum antibiotics on the nasopharyngeal flora will be made.

In an analysis of the age of death of 42 patients who died during the five-year period 1945 to 1954, the average age of death was 45.2 months. This figure is in sharp contrast to the average age at death prior to the introduction of broad-spectrum antibiotics. In the nine-year period ending Jan. 1, 1949, of 57 patients who died the average age at death was 12.8 months.

DISCUSSION

DR. ROBERT KAYE, Philadelphia: I should like to comment on the probable mechanism of the beneficial effects of chlortetracycline on patients with fibrocystic disease. This appears to be the result of its action as an antibiotic on the pulmonary infection rather than as a primary effect on nitrogen metabolism, as suggested by Stowens (*Pediatrics* **8**:60, 1951).

This conclusion follows from the results of a balance study carried out by Dr. McCrory, Dr. Caughey, and myself. In our patient, after the pulmonary infection was brought under control with penicillin, the administration of chlortetracycline did not result in an increase in nitrogen retention.

DR. RUSTIN MCINTOSH, New York: I have recently studied our patients with pancreatic fibrosis who have lived to the age of 10 years or more. Of those on whom we have adequate data, there are 23 now living and 4 who have died. As a group these patients present a number of interesting paradoxes, one of which is the very fact that so many of them are still alive, inasmuch as those who were born 10 years ago or longer did not have the advantage of early administration of any of the antibiotics, on which we now lean so heavily to combat the pulmonary infection.

The fact that some of these patients can live for so long is not especially new. Many of you will recall that one of Parmelee's patients described in 1935 was a girl with steatorrhea, who came to autopsy at the age of 14 years and was found to have the typical pancreatic lesion.

Just what it is that has enabled some of these patients to survive first infancy and then early childhood, only later to be taken under a modern and more nearly effective therapeutic program, is not yet clear; but it is evident that some have done so. When they reach the age of 10 years, some of them are surprisingly well, even though they have not had the advantage of early treatment.

We have one boy, now 16 years of age, who is in high school. In addition to being partly self-supporting, by holding an after-school job, he is a prominent athlete, playing football and taking part in track and baseball. Since he was born long before even penicillin came into clinical use, his survival is not easily accounted for. In addition, there are also two girls who have been quite athletic, one of whom at the age of 10 years fractured a clavicle while playing football.

The prevailing view is that antibiotics play a tremendous part in the survival and welfare of these patients. One can scarcely avoid the feeling that they would be better off if we could keep them from ever having the serious staphylococcal bronchopneumonia, which seems so inevitable in the course of this disease if nature is left to take its course. Possibly we can look ahead to some prophylactic program which will enable us, by catching these patients early, to forestall the pulmonary infection. In that event, the number of healthy survivors, or at least effective surviviors, may turn out to be much greater.

DR MILTON RAPOPORT, Philadephia: Dr. McIntosh has touched on a point which has intrigued most of us who have seen patients with this condition, namely, that the pulmonary complications which have been responsible for the death of the great majority of these patients are said to be complications of pancreatic fibrosis. Reasoning from an analogous situation with which we are concerned, viz, that the higher death rate of nephrotic patients in the pre-chemotherapeutic days and preantibiotic days was largely due to infection, one wonders about the natural history of this disease, pancreatic fibrosis, if you get rid of the pulmonary infection which is responsible for most of the deaths.

Dr. McIntosh has mentioned somebody 16 years of age. I just wonder what would happen if you would get most of this infection under control and there were more survivals to adult life. It poses a rather interesting and slightly staggering thought: If this is a situation with a high genetic incidence in the population, estimated as 1 in 50 as a top figure, carried by heterozygotes, the consequence of keeping these people alive and allowing homozygous persons to breed would be disastrous, to say the least.

DR. CHARLES U. LOWE, Buffalo: Dr. Shwachman seems to have shown his usual care and assiduousness in preparing these data for us to examine today. I assume that the conclusion with which he wishes to leave us is that continuous chemotherapy is essential for the results that he has presented. I wonder whether it would not be appropriate to question Dr. Shwachman as to whether the facts have been presented so as to permit us to accept this conclusion.

As I understand the material, Dr. Shwachman has taken a large group of patients with fibrosis of the pancreas, followed them carefully, and given them all continuous chemotherapy; a large group of these patients have survived. Does this mean they all survived because they received continuous chemotherapy? Would he have achieved comparable good results using

discontinuous chemotherapy? I wonder whether the alternate case method would not be more appropriate to permit us to accept his conclusion. Then one might have compared the results of continuous therapy with those of intermittent therapy.

The second point which I should like to question concerns the age distribution of patients. I believe that all who have followed any number of children with fibrosis of the pancreas have been impressed with the fact that sporadically there appear patients of 10 to 14 years of age who have never come under the care of a physician, have never received any extensive chemotherapy, and yet have survived. On the other hand, we regularly see infants who, even with the most intensive chemotherapy, fail to survive. If this is correct and these two groups of patients exist, it would be important to find out in Dr. Shwachman's group what the average age was of those patients that survived versus the average age of those who died. If Dr. Shwachman is able to present these age-distribution data, I feel that it would be very informative and perhaps lend greater credence to the conclusion which I believe he wants us to accept.

DR. HARRY SHWACHMAN, Boston: I am grateful to Dr McIntosh for pointing out the great variation in the severity of this disease. It is not an uncommon experience to encounter an occasional patient with mucoviscidosis at the age of 8 or 9 years with a relatively uneventful past history. We have recently seen a 30-year-old man, the father of one of our patients, with clear-cut evidences of pancreatic insufficiency. We have under observation a 17-year-old boy with pancreatic fibrosis, who came to our attention in the course of a family investigation. The true incidence of patients with mild disease is unknown. I suspect that it is greater than we currently recognize. A small number of patients with mucoviscidosis show normal pancreatic function early in life, and as they develop progressive pancreatic disease, the digestive enzymes disappear. The pulmonary manifestations do not necessarily parallel the severity or the degree of pancreatic dysfunction. We feel that it is the extent of pulmonary involvement by mechanical means and infectious agents that determines the prognosis. The pulmonary aspect should not be considered a complication of the disease but a part of it. In this connection, I should like to indicate the inadequacy of tests for pancreatic function. The possibilty that other fundamental defects may exist in this disease and may give us diagnostic clues comes from the recent studies on sweat electrolytes from the Babies Hospital. That older persons have survived without treatment indicates the need for recognizing mild cases and classifying them separately in any study concerned with therapy. In reply to Dr. Lowe, I should like to show two slides. The first is a breakdown of our cases which shows the age of onset of pulmonary symptoms, the age at time of diagnosis, the duration of antibiotic therapy, and present age. This slide is contrasted with the results of the series of cases reported by Bodian, which may be used as a control group. We are impressed with the gross mortality figures and the number of patients over 5 years of age in

	Bodian Series	Present Series
Total patients	116	123
Dead	68	22
Living	47	101
Over 5 yr. of age	15	61

our series as contrasted with untreated cases. We have examined our own cases to determine how our present therapy affects age of survival of treated patients. Between 1940 and 1948, the average age at death of 57 patients was 12.8 months. During the 1949-1953 period, the average age at death of 42 patients was 45.2 months. The broad-spectrum antibiotics came into general use in 1949.

Dihydroxyacetone Tolerance Test as a Diagnostic Procedure for Glycogen Storage Disease. DR. WILLIAM COCHRANE (by invitation) and DR. GEORGE M. GUEST, Cincinnati.

More than 20 years ago several investigators suggested that the triose sugar dihydroxyacetone (DHA) might serve as a substitute for glucose in the treatment of diabetes, after experimental evidence indicated that dihydroxyacetone was rapidly metabolized in the body. Linneweh, in 1936, and Raiha, in 1939, devised dihydroxyacetone tolerance tests to aid the differential diagnosis of disorders of carbohydrate metabolism associated with hepatomegaly. They reported that oral administration of dihydroxyacetone led to a rise of dihydroxyacetone in the blood, higher in patients with liver cirrhosis than in healthy children, while in glycogen-storage disease the blood dihydroxyacetone did not rise at all.

Investigating this problem further, we have done similar dihydroxyacetone tolerance tests on infants and children with large livers associated with galactosemia, Niemann-Pick disease, diabetes mellitus, and glycogen-storage disease. In all cases except the latter, the administration of dihydroxyacetone by mouth, 1 gm. per kilogram of body weight, led to variable increases of dihydroxyacetone in the blood. In five children with hepatic glycogen-storage disease, the level of dihydroxyacetone in the blood did not rise. In four of these cases, the glucose level in the blood rose after the administration of dihydroxyacetone, but in the fifth it remained unchanged. In this case, with the most severe physical manifestations (hepatomegaly, dwarfism, albuminuria, etc.), the failure of glucose to rise suggests a defect or absence of the glucose-6-phosphatase enzyme, as in the cases reported by Cori and Cori.

The dihydroxyacetone tolerance test appears to be a useful procedure for the diagnosis and prognosis of hepatic glycogen-storage disease.

DISCUSSION

DR. RICHARD WAGNER, Boston: The presented data seemed to correlate well with the present concept of glycogen-storage disease as a defect of the specific liver glucose-6-phosphatase (Cori and Cori).

Very little is known about the fate of dihydroxyacetone in the normal organism. In its phosphorylated form it is an intermediate of the glycolytic cycle between hexosediphosphate and phosphoglyceraldehyde. Most likely the phosphorylation takes place in the liver.

In glycogen-storage disease, the over-all equilibria of the glycolytic reactions favor glycogen deposition. It may be that after ingestion of dihydroxyacetone, the reaction comes to a standstill at the stage of glucose-6-phosphate, which cannot be dephosphorylated and is synthetized to glycogen. Hence the ingested dihydroxyacetone does not show in the blood. It would be of interest to find out whether or not the increase in reduction found by the investigators is the result of an accumulation of a reducing substance which is only partially fermentable by yeast. We recently studied two cases of glycogen storage disease and found that the reducing substance present in the blood under fasting conditions is almost 100% unfermentable.

DR. BENJAMIN KRAMER, Brooklyn: We recently had an opportunity to study three cases of glycogen-storage disease in newborn infants and one case of so-called idiopathic hypoglycemia.

The diagnosis of glycogen-storage disease was made by taking a biopsy specimen of the liver and making a quantitative determination of its glycogen content. Dr. Gerty T. Cori was kind enough to determine the glucose-6-phosphatase, not only with respect to the amount per gram of liver but also per liver cell.

We tried, as an additional therapeutic as well as diagnostic measure, the effect of a brand of pancreatic gland hormone (Glucagon). We were able to produce transient hyperglycemia in normal children. However, there was practically no effect whatever from the use of this substance in glycogen-storage disease. In fact, Glucagon administration was at times followed by a drop in the blood-sugar level.

DR. WILLIAM COCHRANE, Cincinnati: I appreciate Dr. Richard Wagner's comments, especially since he and Dr. Parnas probably published the first clinical description of glycogen-storage disease of the liver, in 1921. Following Dr. Wagner's work on the increase of glycogen in the white blood cells, we have planned to investigate in Cincinnati the effect of glycolysis of dihydroxyacetone by white blood cells in cases of glycogen-storage disease.

With regard to Dr. Kramer's question, we have not given Glucagon (hyperglycemic factor) to any of our patients. DeDuve and others have administered Glucagon to cases of the hepatic type of glycogen-storage disease without any rise in the blood glucose. Thus the test is very similar to the epinephrine-glucose response in these patients. However, if the defect were not in the enzyme glucose-6-phosphatase, preventing the breakdown of liver glycogen, possibly in the debrancher amylo-1,-6 glucosidase there might be some release of glucose from the stored hepatic glycogen.

Amino-Aciduria in Galactosemia. DR. SYDNEY S. GELLIS, and DR. DAVID YI-YUNG HSIA (by invitation), Boston.

This paper will be published in full in a forthcoming issue of the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN.

DISCUSSION

DR. HAROLD E. HARRISON, Baltimore: This is a quite interesting paper. Metabolism of amino acids or reabsorption of amino acids by renal tubules is receiving more attention now, partly because of better methodology. I wonder about the time relations of the appearance of amino-aciduria. I would think that that might help to determine whether this was competitive inhibition. If it is competitive inhibition, then the amino-aciduria should appear immediately upon saturation of the tubular system with galactose, and one should find the amino-aciduria just as soon as a load of galactose was given.

If, on the other hand, it was an injurious effect, such as that as we have seen with lead and other heavy metals, it might not appear until cumulative toxic effects had resulted.

DR. WILLIAM COCHRANE, Cincinnati: In Cincinnati, two cases of galactosaemia were recently reassessed. One case had been on a milk-free diet for two years, and at the time of examination no abnormal physical findings were found. The second case was almost 2 years old and had been on a milk-free diet since diagnosis at 6 weeks of age and was in excellent health.

Urine specimens were collected prior to a galactose tolerance test (1.75 gm. per kilogram of body weight), at the end of the five-hour test, and two days later. Partition chromatography was done, and it was noted in both cases that the initial specimens revealed a normal amino acid pattern, but the five-hour and two-day specimens contained a marked increase in total amino acid.

I should like to ask Dr. Hsia if he has given galactose in large amounts to normal children and then noted any increased excretion of amino acids. Craig and Maddock's work in giving high galactose diets to rats produced a marked increase in nitrogen excretion and amino-aciduria, but no liver damage.

DR. HENRY L. BARNETT, New York: I think that Dr. Hsia's and Dr. Gellis' interpretation that the increased excretion of amino acids is due to decreased reabsorption by the renal tubules is undoubtedly correct, and it seems to be the case in many instances of amino-aciduria, as Dr. Hsia mentioned.

However, I should like to point out that it is possible to measure glomerular filtration rate, and although an increase in glomerular filtration rate is not very likely to be the cause of increased excretion, one cannot conclude that increased rate of excretion of a substance is due to decreased tubular reabsorption unless one shows that the glomerular filtration rate remains unchanged.

DR. MILTON RAPOPORT, Philadelphia: I should like to point out that one of the factors Dr. Hsia eliminated is the possibility of hypoglycemia, eliminated purely on the basis of analogy; that there were no comparable lesions in pure hypoglycemic states is not entirely valid. This is a somewhat different hypoglycemic state, the hypoglycemia varying in intensity with the hypergalactosemia, with both sugars competing for a similar transport mechanism. The effects of the hypoglycemia in this situation may be much more intense than that in uncomplicated hypoglycemia.

DR. DAVID YI-YUNG HSIA, Boston: I should like to thank the various discussers. We did not do the short-term studies, primarily because we started these studies with the illusion that amino-aciduria was caused by liver damage. We hoped to accentuate this by giving large amounts of galactose over a long period of time so that we could get measurable increases in the serum amino acid levels, but it turned out that they were unaffected. This suggests to us that the amino-aciduria is primarily a renal mechanism.

We have not given galactose to normal children, because we were under the impression that when you gave normal children a great deal of milk, which we have done on various occasions, the alpha amino nitrogen quantitatively does not become altered much. We have measured it in terms of milligrams per pound of body weight for 24 hours, and the average of a group of 20 normal children is about 0.85, with one standard deviation being plus or minus 0.10, so that we did not feel there was enough variation to justify a special study. However, it would make an interesting experiment.

Dr. Barnett's point on glomerular filtration rate is a very important one, which we had a great deal of trouble with in our own minds in evaluating the change of amino acid metabolism in infectious hepatitis. We were not able to convince ourselves completely that all the changes of blood and urine amino acids which do occur in infectious hepatitis were purely due to liver damage and that perhaps a renal factor may not be involved. I think that Dr. Barnett understands the problem.

As to the hypoglycemic state, the only comment I can make is that we did do alpha amino nitrogen studies on one patient with true idiopathic hypoglycemia who did have very low levels of blood sugar, and his alpha amino nitrogen levels were normal.

Can Tuberculosis Meningitis be Prevented by Antimicrobial Therapy? Dr. Edith M. Lincoln, New York.

The results of antimicrobial therapy in complications of primary tuberculosis are excellent. At Bellevue Hospital Center, where many children are seen who have severe tuberculosis, the death rate was 21.5% in the years 1930 through 1946. This fell to 5.0% after the introduction of therapy with streptomycin combined with thiazolsulfone (Promizole) or paraaminosalicylic acid, and since the introduction of isoniazid in 1952, the mortality rate has been further reduced to 1.5%. But streptomycin did not apparently prevent the development of complications, such as meningitis, which continued to develop in many children with miliary tuberculosis even while they were receiving chemotherapy. But isoniazid may differ from streptomycin. In the group of children in Bellevue Hospital Center, no case under treatment with isoniazid for any cause, even for miliary tuberculosis, has developed clinical meningitis, even when tubercle bacilli have been cultured from the cerebrospinal fluid. Careful inquiry among other investigators in this city and abroad has not revealed any instance of clinical meningitis developing while the patient was taking isoniazid. If these observations are substantiated, the use of isoniazid will have to be considered in every child with active primary tuberculosis and possibly also in children with known recent conversion of tuberculin tests, even if chest x-rays are negative. The duration of therapy would be for a year, in order to cover the period during which meningitis is most likely to develop.

Before entering into such an extensive program of antimicrobial therapy in an effort to prevent meningitis, carefully controlled series of children with primary tuberculosis should be studied, in which the cases to be treated are selected at random and all the children are carefully followed for more than a year. Preliminary results of such a program at Bellevue Hospital Center will be reported.

Management of Tetanus: Report of Fifteen Consecutive Cases with Recovery. Dr. Gilbert B. Forbes, Rochester, N. Y., and Dr. Marian Auld (by invitation), Yankton, S. Dak.

The seriousness of this disease is attested by many reports indicating that the case fatality rate, even in recent years, is of the order of 20 to 50%. The purpose of this presentation is, first, to point out the necessity for full realization of the complexity of the therapeutic program indicated in patients with generalized tetanus, and second, to emphasize the importance of one particular aspects of treatment, namely, the maintenance of an adequate airway, as an important factor in prognosis. The former objective has been discussed adequately by a number of authors; the latter has been recognized as essential only in recent years.

The group of patients to be presented represent the experience of the Children's Medical Center of Dallas, Texas, from 1950 through mid-1953. They ranged in age from 1 week to 13 years; two were newborns. Two patients were considered as having a mild form of generalized tetanus, while the rest were classified as severe and moderately severe in character.

The treatment schedule employed will be presented, with particular reference to antitoxin, sedation, general nursing care, and tracheotomy. Only one patient was given a muscle-relaxing agent, mephenesin (Myanesin). In general, emphasis was placed on meticulous attention to the various details of the therapeutic schedule and the maintenance of proper pulmonary ventilation.

On the basis of our experience, it is believed that with strict adherence to certain principles of management, a substantial reduction in case mortality rates can be anticipated.

DISCUSSION

DR CHARLES A. JANEWAY, Boston: I should like to congratulate Dr. Forbes on his paper. I am very happy to hear him say some of the things he does, because they confirm our own experience with this disease almost completely. I don't know any disease, except bulbar polio, which calls for as much careful watching and minute care of the patient, and I am quite sure that the two single most important items in the scheme of treatment which Dr. Forbes outlined are the special nurses and the constant medical supervision.

I was also happy to hear him say that he was able to handle these patients without the use of the muscle-relaxing group of drugs, because this has been a moot point. Our experience has certainly duplicated his in that we have only used them twice, and each time have gotten into trouble.

The fact that one can use a variety of sedatives, I am sure, is true. Because of its convenience, we have used rectal tribromoethanol (Avertin) almost completely ourselves, and, despite the literature, have had patients on tribromoethanol for as much as 30 or more days without any evidence of serious liver damage, except in one patient, where we did substitute paraldehyde after some 20 or more days.

There are one or two other complications which I think are of interest. In one child we observed massive gastrointestinal hemorrhage, which we felt was due to a Cushing's type ulcer as a result of the process going on in the brain, and we have had one or two patients who have shown psychological impairment subsequently.

DR. ROBERT B. LAWSON, Winston-Salem, N. C.: This is an excellent paper, and I would agree entirely that very careful meticulous attention to detail is the secret in treating tetanus.

However, I should like to report that in the last 13 consecutive cases that we have had at Winston-Salem, we have not done any tracheotomies and have had no deaths. I think the reliance on a tracheotomy is liable to be overdone, and I wonder in looking at this chart if some of the respiratory complications, such as atelectasis, may not be greater in tracheotomized patients than in those without tracheotomy.

We believe implicitly that children with tetanus should not be fed by mouth or by gastric tube. We believe in very heavy sedation, but I do not think tracheotomy should be done in as large a proportion as this, in which 10 were done out of 15, and it is stated that two more possibly should have been done. That almost approaches a "routine" tracheotomy.

One question I should like to ask Dr. Forbes. He doesn't say anything about fractures of the thoracic spine. Of our 13 cases, 3 had fractures of the thoracic spine picked up, the last 2 by routine x-ray, the first due to persistent pain in the back. The fractures apparently come from the severe spasm.

DR. EDWARD L. PRATT, New York: I have been interested in this disease for a long time. Actually, it was the medical students who got me interested in it, because they asked so many questions which seemed unanswerable from a survey of the literature.

We reviewed 56 cases. I must say that during that series, when no special form of therapy was applied to some patients, we had runs of as many as 15 consecutive patients with no deaths. So one must appreciate that when you have tetanus, you don't have a particular disease of equal severity, and you must grade your patients, as Dr. Forbes has.

In my own experience, the thing that was most helpful in grading patients was not the incubation period, but rather it was the duration of time from the first symptom that the patient had until he had generalized spasm or convulsion; second, was the amount of sedation necessary to prevent generalized spasms; third, was the impression of the person seeing the patient regularly, and last, the incubation period.

I think one should appreciate that one difficulty in managing these patients is that everyone is aware of the fact that a high number of patients with tetanus die, hence they tend to do too much for the patient. Hypocrates was quite sure that a great many untreated patients survived.

In our own series, there was a patient who was misdiagnosed and had no treatment until his symptoms were subsiding, and yet he had severe enough tetanus to crush three thoracic vertebrae. So I think the evaluation of the severity is very important, both in preventing overtreatment of these patients and in deciding which patients require more attention than others.

I think it is important that these patients have the benefit of skilled anesthetists at all times, if one is to use the muscle-relaxing drugs. Actually, in some of the very severe patients, I think almost complete relaxation and artificial respiration will tide over a few patients who otherwise would die. But I am also sure that the complications that relaxants bring out, particularly in control of respiration and increased secretions, will lead to a lot of unnecessary deaths.

DR. ANGUS M. MCBRYDE, Durham, N. C.: If there is any question, tracheotomy should be done on patients with generalized tetanus. Certainly one should be radical because of the fact that patients with tetanus die of inability to maintain an adequate airway or from aspiration. One must be careful in assuming from history that a child is immunized to tetanus, as we now have on our service a 9-year-old child who developed tetanus seven days after débridement and a booster dose of tetanus toxoid. Investigation showed the child had only one previous diphtheria-pertussis-tetanus injection, at 3 years of age. It had been taken for granted that she received tetanus toxoid in infancy, but this was proved to be untrue. We originally suspected she was one of those rare persons who has no antigenic response to tetanus toxoid.

DR. RANDOLPH K. BYERS, Boston: I should like to add that it is possible, especially with barbiturates, to produce at least functional decerebration to the point where you get increased reflexes in cases of this sort. We had one of these children who now has psychological difficulties and who had such neurological signs on large doses of barbiturates after being treated for a period of about a month. These signs disappeared when he was taken off barbiturates, and it was pretty clear by that time that most of the apparent spasm that occurred late was due more to decerebration, possibly from drugs and possibly from anoxia during his spasms, than it was due to tetanus. It is important to remember that tetanus does not produce neurological signs between attacks.

DR. KATHERINE DODD, Little Rock, Ark.: I should like to ask Dr. Forbes about his two children with tetanus neonatorum. That is the most common type of tetanus we see. It is impossible for us to get special nurses for anything but polio, where the polio foundation pays for them. We find in tetanus neonatorum that our greatest difficulty is that the signs of tetanus last so long that feeding is a great difficulty.

These childen are only 5 to 6 days old. They have usually not regained their birth weight, and they keep on having spasms for sometimes as long as a month and are very stiff. Does Dr. Forbes have difficulty in keeping these children nourished, and if so, how does he do it?

DR. MCGOVERN, Washington, D. C.: I just wanted to ask Dr. Forbes—I was interested in the three cases of serum sickness out of the 15 cases—whether or not the patients were tested for sensitivity first, and what is his opinion with respect to these patients of giving one massive or very large dose of antitoxin first, rather than giving one daily over the period of the illness?

DR. GILBERT B. FORBES, Rochester, N. Y.: I want to thank the discussants for their very kind comments.

In response to Dr. Janeway's question about psychological residua, I am afraid our data will not answer that question. Our follow-up period has not been long enough.

One child had definite residua which we think were related to repeated bouts of anoxia. As far as the others are concerned, we cannot document this effect.

Dr. Lawson's comments about atelectasis and tracheobronchial complications as a result of tracheotomy are pertinent in some respects. The patients in our series that were not tracheotomized were the patients who had milder forms of tetanus. It is impossible to conclude anything from our small series of patients about the tracheotomized group versus the ones who did not have tracheotomy.

It is quite evident in patients with generalized tetanus of the severe form that there are large amounts of tracheobronchial secretions present. This is not a unique finding in our series. This finding in itself is one indication for the procedure.

One is going to have to sedate these patients heavily, and one is going to have to depress their natural cough reflex. One is not going to be able to keep them in an efficient position for drainage of tracheobronchial secretions, and I think in many respects we feel much better about the care of our patients, much more relaxed, once the tracheotomy tube is in place. I do not recommend its routine use, however.

We do not have enough information about cervical spine fractures to answer that particular question.

Dr. Pratt brought up a very pertinent point when he said that in his series of 56 patients there were 15 consecutive recoveries in the group, and I meant to say at the end of my presentation this morning that our 15 consecutive recoveries may be entirely fortuitous. However, we all know that this is a disease of variable severity. There are patients with generalized chronic tetanus who need practically no treatment at all. There are other patients who will die on the first day of treatment unless something very drastic is done.

So I did not intend to imply that the aspects of fortuitiveness were obviated in this series.

Dr. Dodd's question is very pertinent. Fortunately, Dr. Dodd, we only had two newborns to deal with in this series. I don't know how we would have done if there had been more. I think this is a very complicated, a very difficult problem. I have no answer to your question. The more current mortality rate figures reflect the seriousness of the problem in this age group. It is more difficult to maintain parenteral nutrition in small babies.

As far as special nurses were concerned, we were able to persuade the hospital authorities to assign special nurses to these patients, even though the hospital was usually faced with a sizable bill by the time the patient was discharged. We are very grateful, and I'm sure the patients are too, for the cooperation of the hospital administration in this regard.

As far as serum sickness is concerned, we have felt on the basis of experimental data that a single large dose of serum provides a generous amount of circulating antibody and that a satisfactory level of antibody will persist for as long as five or six weeks. We felt, therefore, that there was no logical basis for repeated doses of serum with the added risk of serum reaction.

Hypergammaglobulinemia Associated with Severe Recurrent and Chronic Nonspecific Infection. Dr. Charles A. Janeway, Boston, Dr. John Craig (by invitation), Boston, Dr. Murray Davidson (by invitation), New York, Dr. William Downey (by invitation), New Bedford, Mass., Dr. David Gitlin (by invitation), Boston, and Julia C. Sullivan, M.P.H. (by invitation), Boston.

In the course of investigating the serum concentrations of γ-globulins in children with severe recurrent local infection, five patients with splenomegaly, hepatomegaly, and generalized lymphadenopathy were found to have markedly elevated serum γ-globulin levels. Two of these patients were siblings, and in them splenomegaly was observed before there was any clinical evidence of infection. Four have had and still have debilitating recurrent or chronic infections of the skin or respiratory tract, usually with such common organisms as Staphylococcus proteus or Pseudomonas. The fifth child succumbed to septicemia with a pneumococcus after a long period of nonspecific infection. Pulmonary infection was the most prominent feature in four patients. Biopsy of skin and lymph nodes in two patients; of muscle, skin, lymph node, and liver in a third, and a complete postmortem examination of the tissues in a fourth revealed diffuse mononuclear reaction or infiltration, with prominence of plasma cells, in all the tissues and organs studied. Bone marrow findings were inconstant.

The concentration of γ-globulins in the sera of these patients ranged between 1.9 and 4.5 gm. per 100 cc. electrophoretically, the normal level for children of similar age by this method usually being about 0.6 to 0.9 gm., and frequently less. Immunochemical characterization of the γ-globulins of these patients revealed them to be normal in reactivity with specific rabbit and horse antisera. The administration of bacterial antigens to three of these patients resulted in varied production of specific antibodies, as one might expect in normal children. Agglutinins against bacteria isolated from several of the patients could be found in the sera in variable titers, but the antigen responsible for stimulating the markedly increased production of γ-globulins could not be identified. In comparison, an investigation of children with severe chronic bronchiectasis or with pancreatic fibrosis and chronic pulmonary infection, as well as of children with other types of nonspecific infection, did not reveal the exaggerated γ-globulin response noted in these five cases.

The patients, who appear able to produce antibodies in response to antigenic stimulation but who are nevertheless unsually susceptible to infection of the skin and respiratory tract despite high levels of serum gamma globulins and a morphologic increase in the plasma cells presumed to produce them, present an immunologic paradox, which is accentuated by the fact that several

of them were originally suspected of having agammaglobulinemia. It is not known whether the chronic infection is the cause or the result of the tissue changes, but the occurrence of this condition in two siblings, with enlargement of the spleen prior to evidence of infection, suggests that an underlying tissue change is primary in these two cases at least.

DISCUSSION

DR. LEWIS THOMAS, Minneapolis: Theoretically, these patients should be able to manufacture larger amounts of specific antibody than normal persons. I wonder whether, in the course of these immunological studies, an investigation of the bactericidal property of whole blood or serum was undertaken. There is some evidence in the literature suggesting that, especially in the case of Gram-negative micro-organisms, it is possible to have complete loss of the bactericidal property with excessive concentrations of antibody, due to a state equivalent to a prozone.

I should also like to know whether the levels of complement in these patients were normal.

Third, I wonder whether the presence of these extraordinary accumulations of plasma cells, all presumably making antibody of one kind or another, might in the presence of systemic infection bring about concentrations of micro-organisms in the tissues containing plasma cells by a mechanism analogous to the specific attraction of bacteria to plasma cell surfaces which has been shown to take place in vitro. I should like to ask whether there were unusual accumulations of the infecting organisms in the tissues containing heavy concentrations of plasma cells.

DR. ROBERT GOOD, Minneapolis: I should like to congratulate Dr. Janeway for bringing together this group of interesting patients. We have been struggling with a similar group of patients who fit the criteria outlined here this morning. The four children we have studied at Minnesota and the three that Dr. Thomas Good has studied at Utah were discovered to have hypergammaglobulinemia and extreme susceptibility to infection while we were searching for patients with agammaglobulinemia.

Although our patients have been troubled primarily with recurrent staphylococcal infections, on occasion the intercurrent disease is due to another micro-organism, such as Proteus, Pseudomonas, or Salmonella. In almost every instance, if my recollections are correct, the history of trouble goes back to birth or shortly thereafter. One of the patients, I recall, suffered from osteomyelitis in the neonatal period and had one infection after another from that time forth. Another developed necrotizing lesions of the skin as an infant, and the repeated or constant respiratory infections proved a problem.

The gamma globulin concentration in these patients ranged from 1.5 to nearly 6 gm. per 100 cc. Two of the children have had rather marked eosinophilia.

We have convinced ourselves that the bone marrow of this group of children is characterized by the occurrence of excessive numbers of plasma cells. Indeed, sometimes, the marrow shows a striking plasmacytosis. Because of the demonstration by Hall and co-workers that myeloma patients producing large amounts of abnormal globulin are sometimes unable to make antibody, we have wondered whether these patients are similarly handicapped. It seems possible that this disease is in some manner a dysgammaglobulinemia and that these patients form either abnormal antibodies or incomplete antibodies. It is also possible that the tremendous hypergammaglobulinemia represents a rather specifically directed immune response which might result in inhibition of the development of other immune bodies.

I would be interested to know whether Dr. Janeway has investigated the capacity of these patients to form antibody against pneumococcal polysaccharides.

DR. JOSEPH STOKES JR., Philadlephia: This very interesting group of cases could have what may be termed a relative immunopenia, that is, an inability to produce antibodies against certain antigens and larger amounts against other antigens. This would fit in well with work that will be reported here later this morning from the Children's Hospital of Philadelphia.

DR. VINCENT KELLEY, Salt Lake City: The cases which Dr. Janeway showed could just as well have been three cases that we had in Salt Lake City. These cases were very similar to those that Dr. Janeway has described.

Two of the three cases that we have had were referred to us as agammaglobulinemia. Two had electrophoretic patterns done before referral which reportedly substantiated the clinical impression of agammaglobulinemia. When we repeated the electrophoretic patterns, they showed hypergammaglobulinemia. They did show the prozone phenomenon mentioned, and I think

probably the interpretation of agammaglobulinemia on the outside was on the basis of not having done mobilities of the electrophoretic fractions, so the interpreters could not be sure which peak was gamma globulin.

An interesting thing that we found in two cases was that the circulating corticosteroids were zero. It seems to me this may be an important factor in the formation of antibody. It is well known that the rheumatic fever patient shows excessive antibody production to the Streptococcus, at least, and rheumatic fever patients also have very low levels of circulating steroids. I wonder wheher this could be a parallel situation.

I should like to ask Dr. Janeway about the rash in these two patients; from the very brief description and from the picture, I wonder if is is possible that this is the typical rash one sees in juvenile rheumatoid arthritis rather than erythema multiforme. The patient with juvenile rheumatoid arthritis can present a picture quite like this, and I was wondering about the possibility. This diagnosis was considered in all of our cases and finally discarded.

DR. C. HENRY KEMPE, San Francisco: We have recently studied a child similar to that of Dr. Janeway and Dr. Kelley, who showed a very low neutrophile count. I think Dr. Janeway may have skipped too lightly over the neutropenia that these children have in common, and I should like to know how severe the neutropenia was in his series. In our case it has been very marked and prolonged for three years in a child who is now 4 years old. She never has more than 4% to 5% neutrophiles, and the total white blood cells are less than 3,000.

Isn't it perfectly amazing that children with such severe bacterial infections would have such chronic neutropenia. It is quite possible that neutropenia is primarily an expression of an aplastic disease and that the gamma globulin response is an agonal ineffectual attempt to overcome that portion of the defect of the immune mechanism by producing more of the other protective substance. This gamma globulin, however, is ineffectual by being qualitatively deficient in specific neutralizing antibodies, even though qauntitatively it is increased.

This would mean that Dr. Janeway's case is really a dysgammaglobulinemia primarily; in other words, a qualitative defect exists, and it does not really matter whether the actual quantitative level is normal, high, or low. Since this gamma globulin is not normal, it is likely that these children would benefit by very large amounts of normal gamma globulin therapy. Such an improvement appears to have occurred in our own case.

DR. BENJAMIN M. KAGAN, Chicago: It is obvious that Dr. Janeway's report elicited a lot of interest.

About 15 years ago, I reported a study of hypergammaglobulinemia done mostly on adults at the Johns Hopkins Hospital. It was very impressive in that study that some of the highest levels were seen in patients with pulmonary infections, particularly with staphylococcal infections, lung abscesses, and bronchiectasis. It is interesting that patients with similar infections elsewhere in the body usually do not have such markedly elevated gamma globulin levels.

Recently, we have been studying gamma globulin in children with mucoviscidosis with chronic staphylococcal lung infections, and we have not found similar large increases.

With the opportunity that Dr. Janeway has in Boston, I am sure he has had experience with such patients, and it would be nice to know what gamma globulin levels he has seen in chronic pulmonary infection associated with mucoviscidosis.

DR. JOHN A. ANDERSON, San Francisco: I got up to cover the country, but Dr. Kempe beat me, and that is the way it always is out there between Stanford and the University of California.

In fact, two of the three questions I wished to ask, he has already covered. One is relative to the leucocytes, and second to a case that we had; hepatomegaly and splenomegaly had a significant eosinophilia, which made us think of one relating to a fully granulomatous question.

The question, Dr. Janeway, is, was an observation of intense repeated and recurrent infections in which the lipid also migrated with the gamma globulin made? I wondered if you had observed or had an opportunity to observe a lipid disarray in the electrophoretic pattern.

DR. HERBERT A. WENNER, Kansas City, Kan.: Dr. Janeway's remark reminded me somewhat of infection with Histoplasma capsulatum. I am interested to know whether he has done skin tests with histoplasmin on the living patients and whether a search was made for Histoplasma at postmortem examination or in tissues obtained at biopsy.

DR. RALPH V. PLATOU, New Orleans: We in Louisiana have a syndrome similar in many respects. I cannot resist asking Dr. Janeway if, among these patients with remarkable hypergammaglobulinemia, any search has been made epidemiologically or by biopsy for the larvae of a number of nematodes which have produced in our experience a clinical picture very similar in many respects to that which he describes.

DR. ALFRED H. WASHBURN, Denver: There are two or three items that interest me here. One is Dr. Janeway's comment about the possible hereditary factor. We are studying a group of average children from middle-class families. One of the things we are doing is determining the protein fractions in the plasma and serum. We have been tremendously struck with the sibling similarity in the persistent levels of gamma globulin in the blood, and if Dr. Janeway has any more evidence for possible hereditary factors in the type and level of the globulin fractions, I should love to hear it.

Then I was interested in the fact that he dealt so briefly with the problem of the antibiotics. I presume most of you know that the average child in the ages between, let us say, 2 or 3 and 6 or 8 years runs somewhere between 5 and 10 respiratory tract infections a year in our average American city, the Cleveland group and our group being very similar.

We were tremendously interested in the fact that we have within our supposedly average healthy children a major group in whom there is a nice correlation between low incidence of respiratory infections, persistently high levels of gamma globulins in the serum, and enlarged lymph tissue with their infections. That is, presumably, a good response in terms of increase in activity of the lymph tissue as shown by palpable lymph nodes, lymph nodes shown in the x-ray, and so on.

We have, however, a minority group who have low gamma globulin levels and a very high incidence of infections. So far most of these have had, from our standpoint, a large amount of antibiotic therapy from infancy right on out, and we are somewhat concerned with the fact that this entity was not seen before the days of antibiotics. I don't know the answer, I merely raise the question. I should like to have Dr. Janeway's reaction to the question of whether it may well be that the frequent and continued giving of antibiotics is playing a part in this picture; not implying that it is the only factor. May it not be that there are certain cases which had better not get so many antibiotics.

And then, finally, one more point, if I may, and some of you may have heard me talk on the point before and will probably smile, but I want to know what is meant by "leucopenia." In a 4- or 5-year-old child, a total count of 5,000 or 6,000, with a very low neutrophile count, is well within the normal range. I would suspect perhaps some of these youngsters simply do not have the usual response of increase in neutrophiles.

DR. JOHN CRAIG, Boston: I might answer some of the questions put to Dr. Janeway with regard to the pathologic findings. In answer to Dr. Stoke's question, I believe that we can agree that a high proportion of the lymphoid cells are an immature type in these cases. There are also immature mononuclear cells, as well as large numbers of immature plasma cells.

The foci of the bacteria which were mentioned were quite prominent in the lung, and one of the cases at autopsy did have an active bronchiectasis.

We did not observe any histoplasmosis. We had in at least four instances bone marrow aspirations and bone marrow biopsies done during life, and with the exception of the increased numbers of plasma cells, they were essentially normal. There was no visceral granuloma seen. The adrenals were normal.

DR. CHARLES A. JANEWAY, Boston: The response to this paper has been what I hoped it would be, only even better, and I am extremely grateful, because it is only by sharing this kind of experience that we are going to get down to what actually is going on.

In response to Dr. Thomas' question about complement, we have data on one or two of the children, and the complement was completely normal. As to the bactericidal power, we do not have data on that.

If Dr. Gitlin is in the audience, he may be able to answer Dr. Good's question about the response to pneumococcal polysaccharides. I am not sure of his results, although I know he has immunized one of the children with Type 3 polysaccharide.

I don't know about the question of the rash which Dr. Kelley raised. I should say that these rashes were not specific for rheumatoid arthritis. I have a feeling that I can tell rheumatoid arthritis by the rash. To me this rash is a little more florid, and the lesions are larger, but this is, as you can see, a matter of clinical impression. Certainly the children have had no joint disease at any time, despite a pretty long course, so it seems unlikely.

As for the problem of the neutropenia, I am delighted to have Dr. Washburn give us normal standards. We are studying, as many of you are, children who don't respond well to infection or who keep getting infections all the time. This is an obvious sequel to our interest in agammaglobulinemia, and there are a number of children with cyclic neutropenia under observation by Dr. Diamond and his group. One is associated with agammaglobulinemia, but most of them are not. These children don't have striking neutropenia or true agranulocytosis, but they tend to have rather lower than normal levels and somewhat higher than normal levels of the monocytes as compared with most of the children we see. It may well be this is simply a reflection of a poor response.

In response to Dr. Kagan's question, I can say that Dr. Gitlin has studied the serums of a large number of children with mucoviscidosis and a large number with bronchiectasis, and they do not have these very high levels of gamma globulin.

Certainly histoplasmosis and all sorts of diseases which we know stimulate the reticuloendothelial system may be associated with extremely high levels of gamma globulin in the blood. We also know that the disease which perhaps borders on neoplasia, multiple myeloma, and its precursors does the same sort of thing.

Is this a response, or is this cell growth going wild? That is the first question which has to be answered. Obviously, many stimuli can result in this type of response. To me, the most provocative thought is that there may be children who cannot produce specific kinds of antibodies. That has been my feeling about these children right along, that they may produce abnormal gamma globulins in the sense that they are ineffectual in the antibody mechanism. Thus, there may be specific defects in antibody formation, as well as the total one, which we call agammaglobulinemia.

The other stimulating thought is Dr. Washburn's, that these children have received striking amounts of antibiotics. Can this reflect in some way either the interplay of massive antibiotic therapy and infection in altering the immune response, or can this possibly represent a hypersensitivity response to prolonged antibiotic therapy in a small relatively susceptible group?

It reinforces my own clinical conviction that I should not give antibiotics to children with respiratory infections unless they are quite sick.

Periarteritis Nodosa in Infancy. Dr. Samuel Kaplan (by invitation), Dr. Louis E. Cimino (by invitation), Dr. Pearl M. Zeek (by invitation), and Dr. George R. De Muth (by invitation), Cincinnati.

Although periarteritis nodosa is a well-described disease in adults, this abnormality has not been recognized during infancy. The clinical features and pathological findings of four cases of periarteritis nodosa in infancy will be presented. The patients were under the age of 6 months at the time of death. In three instances the disease was rapidly fatal and occurred as an acute illness in an apparently well baby, with death in less than 10 days.

The criteria for classifying the various types of necrotizing angiitis have been presented in previous reports by one of us. In the present series one case of primary periarteritis nodosa presented widespread, and grossly visible, nodular arterial lesions that caused death at 5 months of age by coronary occlusion. The other three cases presented massive renal infarction, embolic in origin, and widespread early lesions of secondary periarteritis nodosa. In two cases, the emboli arose from thrombosis of the ductus arteriosus and in the third, from a cardiac mural thrombus. These and similar cases from the literature suggest renal injury as a factor in the pathogenesis of periarteritis nodosa.

Varying degrees of pyrexia and hyperpyrexia occurred in all instances. Although the cardiovascular system was involved in all patients, symptoms and signs of involvement of this system were striking by their absence. However, mild cyanosis and dyspnea were present in all instances, but there was no evidence of congestive heart failure or cardiac enlargement; murmurs were absent, and electrocardiograms were normal.

Involvement of the gastrointestinal system was manifest by varying degrees of hematemesis and/or melena. The kidneys were palpable in three cases, and these patients also exhibited albuminuria and hematuria. Hepatomegaly was present in all cases, and the testes were enlarged in one patient. The clinical signs of meningeal irritation were present in two cases. Examination of the blood showed leucocytosis, terminal anemia from hemorrhage, and an elevated nonprotein nitrogen.

Mechanisms Involved in the Production of Fibrinoid Necrosis by Endotoxins. Dr. Lewis Thomas, Dr. Robert A. Good (by invitation), and Dr. Richard T. Smith (by invitation), Minneapolis.

The basic lesion in the so-called "collagen" diseases is the deposition of fibrinoid material in tissues. The prototype of this group of disorders is disseminated lupus erythematosus, in which extensive deposits of fibrinoid occur in the lumen and walls of blood vessels and in surrounding connective tissues. The closest approximation to this histopathological situation obtainable in experimental animals is the generalized Shwartzman reaction, which is produced in rabbits by two intravenous injections of endotoxin from various Gram-negative bacteria. Within a few hours after the second injection, masses of material resembling fibrinoid appear in the glomerular capillaries, resulting in bilateral cortical necrosis of the kidneys. Under certain conditions, similar material appears in the coronary arteries, in association with varying degrees of necrosis of the vessel walls, and it also occurs as vegetations in the mitral and aortic valves. Photomicrographs to illustrate the similarities between the human and experimental lesions will be presented.

Serial histological studies of kidneys during the development of the generalized Shwartzman reaction showed that fibrinoid appears within the lumen of glomerular capillaries before there is any evidence of vessel wall damage or necrosis. It is considered probable that the material is derived from the circulating blood. Histochemically it has the reactions of a glycoprotein, in fixed sections. In fresh unstained preparations of isolated glomeruli obtained by fractional centrifugation from homogenates of necrotic cortical tissue, the glomeruli exhibit intense birefringence in polarized light. Normal glomeruli are not birefringent. The birefringence disappears rapidly when trypsin or papain are added to the suspension and after acidification. Glomeruli exposed to alkali do not lose birefringence.

Two agents with the property of combining with fibrinogen and forming insoluble precipitates have ben reported by others to produce glomerular capillary occlusion, with eosinophilic material which resembles that seen in the generalized Schwartzman reaction. These are a highly polymerized dextran sulfonate (Walton and Squire), and sodium polyanethol sulfonate ([Liquoid] Dreyfus & Hausman). It is conceivable that an analogous event may occur in the generalized Shwartzman reactions, which would be consistent with the protection by heparin demonstrated in this laboratory. Preliminary observations indicate that large doses of a streptokinase-streptodornase mixture inhibit the development of renal cortex necrosis. Experiments employing plasmin activated by streptokinase are now in progress.

If the formation of an insoluble or precipitable material in blood is a stage in the development of the glomerular and arterial lesions of the generalized Shwartzman reaction, it is probable that the distribution and intensity of lesions would be influenced by vasomotor changes in tissues. The pronounced changes in blood vessel function which are caused by endotoxin are therefore of much interest. Intravenously injected endotoxin produces an intense degree of vasocostriction, with brief intervening periods of vasodilatation, lasting several hours. After this there is a state of hyperemia which involves many organs, including the skin. It has been found that the local vasoconstricting effect of epinephrine is greatly augmented by endotoxin. Animals given intradermal epinephrine and meningococcal endotoxin by vein develop large areas of hemorrhagic necrosis in the skin. Also, the injection into the skin of a mixture of epinephrine with endotoxin produces lesions indistinguishable from the local Shwartzman reaction.

In contrast, vasopressin injection (Pitressin) caused extremely severe systemic reactions but no local reaction in the skin. The intravenous injection of vasopressin injection in animals given endotoxin 24 hours earlier resulted in rapidly developing reactions of paralysis and coma. Animals which survived this event developed extensive cardiac lesions, with fibrinoid necrosis of the arteries and valves, pericarditis, and necrosis of muscle fibers.

DISCUSSION

DR. VINCENT KELLEY, Salt Lake City: To me this is a very exciting paper. I think that Dr. Thomas and his group are getting very close to some answers in these diseases. I have a couple of questions that I should like to have clarified.

As most of you know, the mucoproteins, the serum polysaccharides, and the serum hexosamines are all elevated in all these diseases in which fibrinoid is deposited, including in addition to the ones Dr. Thomas mentioned, lipoid nephrosis and practically all of the related diseases.

Have you done any studies in which you have precipitated the cold-precipitable material and then measured the mucoprotein, polysaccharide, or hexosamine? Are these substances precipitated out of the blood, and do they represent the material that you are measuring?

The concentrations of your material correspond in general to those that we find of mucopolysaccharides, whether they are measured as mucoproteins, or whether they are measured as the polysaccharides themselves, in acute rheumatic fever, in lupus, and in all these diseases.

Dr. Glick and his group feel there is at least a relationship between heparin and the nonspecific hyaluronidase inhibitor which is elevated also in these diseases. Do you think that it is possible, or would you care to speculate upon the relationship of the hyaluronidase inhibitor to the mucoproteins, and so on, in the formation of fibrinoid?

DR. JOHN CRAIG, Boston: There are several questions that I should like to ask. One, what is the level of the platelets during the reaction seen here? We have noticed in very recent months two young infants who show identical lesions in their glomeruli; they have the same plugging material, and both of these children had severe thrombocytopenia at the time.

Second, I should like to know whether fat stains were done on this material? In our two cases, a large amount of fat was demonstrable in these glomeruli. Also, I should like to know whether specific fibrin stains were done, whether, for instance, a phosphotungstic acid hematoxylin stain showed the presence of fibrin, because it appears that you can often have this material precipitated in glomerular capillaries and yet have a negative stain for fibrin.

DR. FREDERICK C. MOLL, Seattle: I should like to ask a point about trypsin reversing the changes he finds in experimental animals. The reason I ask this is because the trypsin inhibitor which we have been able to show is elevated following the administration of cortisone following sterile abscesses and other methods of stress. I wonder if they have had an opportunity to study this factor in these.

DR. CAROLYN F. PIEL, San Francisco: In working with nephrotoxic serum disease in rats, we have found fibrinoid thrombi similar to that described by Dr. Thomas in the glomerular capillaries.

I should like to ask Dr. Thomas two questions. You previously reported that heparinization interfered with production of the renal lesions of the generalized Shwartzman reaction. What is the mechanism of heparin there? Does it remove this precipitable material beforehand?

Also, in referring to the patient with lupus, did this patient have the nephrotic syndrome in association with the fibrinoid material in the glomerular capillary loops?

DR. WALLACE W. MCCRORY, Philadelphia: I should like to ask Dr. Thomas whether this process can be produced to a less degree. My reason for this question is that I get the impression from this that the kidney is developing the lesion because of the peculiar anatomic structure of the glomerulus; in a sense, I am asking, is the demonstration of the plugging of the glomerulus related to the development of a certain level of material in the circulating plasma?

The reason for this, I think, is quite obvious. Can you get this to a mild degree, which would seem to be the situation one would be dealing with when carrying it over to the human, rather than the massive Schwartzman?

DR. LEWIS THOMAS, Minneapolis: Dr. Piel has asked how the prevention of the generalized Shwartzman reaction by heparin can be related to the demonstration of the heparin-precipitable protein which appears in plasma after an injection of endotoxin and how, in the same terms, we can account for the production of the generalized reaction by heparin-like polymers of large molecular size.

I think it is a matter of competition. We have observed that heparin uniformly prevents the reaction to sodium polyanethol sulfonate and dextran sulfate in endotoxin-treated animals. We believe that heparin may combine competitively with the protein which appears after endotoxin,

and the combination is sufficiently stable that it remains soluble at body temperature. At low temperatures, as we have shown, the complex formed between heparin and the protein is insoluble, and a precipitate is formed. We think that the appearance of fibrinoid after injection of the synthetic polymers is due to their combination with the same protein in the blood, with precipitation in vivo.

As to the question concerning trypsin, we have not been able to demonstrate any effect of proteolytic enzymes in the generalized Shwartzman reaction. Trypsin and papain will remove the birefringent protein material in the glomerular capillaries in vitro, but have no effect on the deposition of the material when injected into the living animal.

The question as to whether vascular lesions of less degree can be produced with endotoxin may be answered yes. We have observed many animals in which minor degrees of fibrinoid deposition occur. We have not succeeded, however, in producing a progressive disease. All of the pathological events become complete within a period of less than 48 hours.

The platelet counts fall to thrombocytopenic levels after either one or two doses of endotoxin. However, we do not find platelets entrapped in the material in the glomerular capillaries, and we do not think it represents a platelet thrombus. There is an obvious pathological resemblance between the animal lesions and those of so-called thrombotic thrombocytopenia, but I would question whether some of the lesions described as platelet thrombosis in the human disease may not actually be vascular occlusion by material similar to that described here as fibrinoid.

Fat stains performed on the fibrinoid deposits in the kidney were negative.

I am afraid that I cannot answer Dr. Kelley's question. We are also tempted by the coexistence in the plasma in the acute phase of the collagen diseases of high levels of mucoprotein and high levels of the hyaluronidase inhibitor which has been shown by Dr. Glick almost undoubtedly to contain a considerable amount of heparin, and perhaps the coexistence of these two materials in blood may be related to the deposition of fibrinoid in blood and in tissue.

Vaccinia Gangrenosa Treated with Hyperimmune Vaccinia Gamma Globulin. DR. GIULIO J. BARBERO (by invitation), ALAN GRAY, PH.D. (by invitation), DR. T. F. MCNAIR SCOTT, Philadelphia, and DR. C. HENRY KEMPE (by invitation), San Francisco.

A progressively necrotizing localized reaction to a vaccination can occur as a very rare complication of vaccination. In the blood of one reported patient and of the patient to be described, no circulating antibodies against vaccinia virus were found.

The patient, K. A., was admitted on April 6, 1953, with the following history. He was vaccinated for the first time at 5 years of age, on Jan. 15, 1953. There was a primary reaction after seven days, which became progressively larger and ulcerated. The lesions continued to spread in spite of local and systemic antibiotics and surgical débridement and excision, until it involved the entire left deltoid muscle with numerous surrounding satellite lesions filled with creamy purulent material. The entire left arm became swollen and edematous. Additional isolated lesions developed on the scalp and lower left arm. On admission, in addition to the above, there was an erythematous swelling of the metacarpal of the right hand diagnosed by x-ray as an osteomyelitis with periosteal elevation.

Vaccinia virus was isolated from the lesions of the left arm in the chick embryo chorioallantoic membrane. The virus was identified by (1) characteristic plaque formation on the chick embryo chorioallantoic membranes, (2) presence of intracytoplasmic inclusion bodies in the membrane plaques, (3) cross neutralization of the patient's virus with vaccinia immune rabbit serum. Vaccinia virus was isolated from a biopsy specimen of osteomyelitic area, and Guarnieri bodies were seen on section. A reversal of serum albumin-globulin ratio was found and a normal level of gamma globulin by electrophoresis.

On April 12, 1953, 10 cc. of hyperimmune vaccinia globulin was given intramuscularly. Two days following injection of gamma globulin, granulation tissue began to appear. This was accompanied by decrease in the purulent secretion. The gamma globulin was given at two-week intervals and was accompanied by a slow regression of the ulcerated areas. The osteomyelitic process of the right hand regressed along with the remainder of the picture. On the chick embryo membranes, the vaccinia plaques were diminished within a week after the onset of treatment. A total course of five 10 cc. doses of hyperimmune vaccinia gamma globulin was given. On July 1, 1953, the cultures were negative, and the gamma globulin was discontinued. The

ulcerated area slowly filled in with granulation tissue, was grafted, and now remains only as a scarred area on the left shoulder. The patient has remained well to the present time and has returned to full activity.

Neutralization tests on the chorioallantoic membrane, using a 50% reduction in pock count as the end point, were performed with several specimens of the patient's serum against both a standard vaccine virus and the patient's own virus. Before the administration of gamma globulin, there were no detectable neutralizing antibodies. Three weeks after the last dose of gamma globulin, the titer was again below detectable levels. During the period of gamma globulin administration, each serum tested showed measurable antibodies, although of low titer (1:2), against both viruses. The bloods were routinely tested just before each dose of gamma globulin.

The patient is presented as the only reported instance of a recovery from this unusual complication of vaccination with evidence indicating that the result was probably due to the hyperimmune vaccinia gamma globulin.

DISCUSSION

DR. CHARLES A. JANEWAY, Boston: I should like to ask one question in the hope that somebody can enlighten me. It is my impression that vaccine virus supplied to the profession in recent years, particularly since the large outbreak in New York, has been considerably more potent than it used to be. I wonder if anyone who is familiar with this problem can tell us if what I think is correct, namely, that new methods have been put in for stepping up the potency of vaccine in its routine preparation, and whether possibly the recent recognition of this problem may not be due to the fact that we are dealing with considerably more potent virus today than we were in the period between the two wars.

DR. ROBERT GOOD, Minneapolis: I want to congratulate the authors on this very nice piece of research work. It is conceivable to me that this sort of lesion in properly disposed patients may not be limited to the vaccinia virus.

We have observed two patients at Minnesota in whom a similar process occurred. These children were not vaccinated. Although we could not establish the etiology or the pathogenesis of the clinical disease observed, the lesions were so strikingly similar to those described here that it seems conceivable that similar reactions may occur upon infection with other viruses. Of course, the possibility that secondary infection with staphylococci capable of liberating necrotizing toxins in persons unable to resist their action is responsible for both groups of lesions must be kept in mind.

DR. GIULIO J. BARBERO, Philadelphia: It is particularly exciting to hear the cases about which we have just previuosly heard from Dr. Kempe and Dr. Lawson; this certainly further implements the value of this particular report.

I want to thank Dr. Janeway for his comments. I have no knowledge about the vaccinia viruses' potency increase. I should wonder whether this would not result in more cases of generalized vaccinia in the beginning, rather than just prolonged vaccinia gangrenosa of the type that has been described.

Dr. Good's comments are certainly exciting, because they bring into focus an entire new field of the specific inability of developing individual antibodies, rather than just to the large group of gamma globulins with which we had previously been impressed.

There is one thing on which there might be comment from the cases that were shown just now. There seem to be different types. In one of the patients, the patient first shown by Dr. Kempe, the lesions seemed to be less ulcerative and more gangrenous. This might implicate more of a capillary type of involvement. Others, like ours, seem to be more destructive.

The other thing also brought up is that there seems to be a division here into a group with agammaglobulinemia and one with normal levels of gamma globulins.

We hope that this report will induce other investigators to use hyperimmune gamma globulin in order to demonstrate what value this agent might have in this lethal complication of vaccination.

I know it has been an exciting adventure in which the East and West have gotten together to get a patient well.

(To Be Concluded)

Abstracts from Current Literature

Newborn

EFFECTS OF WITHHOLDING FLUID IN THE IMMEDIATE POSTNATAL PERIOD. JOHN D. L. HANSEN and CLEMENT A. SMITH, Pediatrics **12**:99 (Aug.) 1953.

These studies were undertaken primarily to evaluate the importance of fluid intake soon after birth and to determine whether consequences of its omission are modified by the relative excess of water in the body of the newborn infant. Weight losses, outputs of Na, K, Cl, N, and water, and serum concentrations were investigated in nine infants having no intake of water for 72 hours after birth and in nine controls receiving approximately 50 cc. of water per kilogram of body weight daily. In seven other infants, 2.5 to 10% dextrose was added to the water intake of the first three days.

The results may be summarized as follows:

1. The amounts of electrolytes and nitrogen excreted in the urine were unaffected by water intake. Thus, infants of gestational age of 36 weeks or more excreted averages of about 0.3 mEq. of Na, 0.45 mEq. of K, 0.35 mEq. of Cl, and 80 mg. of N per kilogram of body weight daily during the three days after birth, whether or not water was provided. The average weight loss of 13% in three days without water intake as against the 8% average weight loss when water was given indicates the greater loss of body water necessitated if fluid is withheld.

2. Five infants of gestational age of less than 35 weeks excreted amounts of electrolytes two to three times as large (and somewhat larger amounts of nitrogen) per kilogram of body weight as did the more mature infants. Again, the excretions were uninfluenced by water intake. The weight losses of these more premature infants were increased by omission of water intake to about the same degree as those of the less premature or of the full-term ones similarly restricted.

3. In infants of all gestational ages studied, omission of water produced a rather uniform increase in urine concentration; the highest osmolarity, 680 milliosmoles per liter on the third day, was in the urine of a premature infant. Concentrations of Na and Cl in the serum and of B. U. N. rose in all infants not receiving water, again without regard to maturity.

4. A comparison on the basis of surface area of measurements obtained for infants with values which have been established for adults showed that daily losses of body weight, and thus of body water, were approximately similar for infants and for adults during fasting with and without water intake, but that outputs of electrolytes by the infants were relatively reduced.

5. The provision of water and dextrose to infants, either on the fourth day after birth or instead of water alone during the first three days, resulted in conservation of body water, but no sodium or nitrogen sparing was demonstrated.

While possible explanations of these various results are considered, it seems reasonable to draw a few broad and clinically applicable conclusions here. The composition of the infant at birth affords no protection against the chemical consequences of water deprivation. Age-conditioned limitations in concentration of urine result in inefficient conservation of body water, and, therefore, in the occurrence of hemoconcentration before it would take place in the adult. Although they were thus unable to maintain homeostasis, the clinically satisfactory status of the infants studied and their prompt return to normal hemoconcentrations after one subsequent day of water and dextrose administration suggest their tolerance of three days without water intake. When fluid is given during the immediate postnatal period, the results suggest that body water will be conserved if the fluid is dextrose solution rather than plain water.

FROM THE AUTHORS' SUMMARY.

ASSOCIATION OF ESCHERICHIA COLI SEROGROUP 0111 WITH TWO HOSPITAL OUTBREAKS OF EPIDEMIC DIARRHEA OF THE NEWBORN INFANT IN NEW YORK STATE DURING 1947. ERWIN NETER, ROBERT F KORNS, and RAY E. TRUSSELL, Pediatrics **12**:377 (Oct.) 1953.

Escherichia coli serogroup 0111 was isolated in 1952 as the predominant coliform organism from five fecal specimens obtained from seven infants who suffered from epidemic diarrhea of the newborn during two serious hospital outbreaks of this disease in 1947. The specimens had been preserved at a temperature of —40 to —70 C. for five years. The association of certain serogroups of Esch. coli and epidemic diarrhea of the newborn infant is discussed.

FROM THE AUTHORS' SUMMARY.

INCIDENCE OF RH ANTIBODY FORMATION IN FIRST PREGNANCIES: OUTCOME OF PREGNANCIES IN 23 CASES NOT PREVIOUSLY SENSITIZED TO RH ANTIGENS. OTTO HARTMANN and O. J. BRENDEMOEN, Acta pædiat. **42**:20 (Jan.) 1953.

In a series of about 75,000 unselected pregnant women, 520 were found to have Rh antibodies; 63 of these patients had received blood transfusions, and 457 had apparently been sensitized by pregnancy alone. Of these 457 women, 23, or 5%, were primigravidae. Serious hemolytic disease occurred in seven of the infants born to these mothers, and four other infants died. Routine testing for Rh antibodies in Rh-negative primigravidae is therefore desirable.

FROM THE AUTHORS' SUMMARY.

Acute Contagious Diseases

THE USE OF THE ELECTROPHRENIC RESPIRATOR IN THE MANAGEMENT OF RESPIRATORY DIFFICULTY IN POSTMEASLES ENCEPHALITIS. LOUIS WEINSTEIN and CHARLES G. COLBURN, J. Pediat. **42**:530 (May) 1953.

Weinstein and Colburn describe four children who developed convulsions and irregular breathing during the acute phase of postmeasles encephalitis.

The convulsions were treated with parenteral phenobarbital followed by diphenylhydantoin (Dilantin) for five or six days.

In each case, the electrophenic respirator restored breathing to normal in a few hours' time. Its use was unquestionably lifesaving.

MACDONALD, Pittsburgh.

EPIDEMIC OF POLIOMYELITIS IN 1952 IN COPENHAGEN: 349 CASES WITH RESPIRATORY DEFICIENCY AND DEGLUTITION PARALYSIS. H. C. A. LASSEN, Presse méd. Supp. 81, p. 1667 (Dec. 19) 1953.

During the last months of 1952, a severe epidemic of poliomyelitis broke out in Copenhagen. It was characterized not only by its importance but also by the large number of cases complicated by respiratory deficiency and deglutition paralysis (349 cases out of 3,000), the respiratory deficiency proving particularly grave in one-third of the paralyzed patients.

At Blegdam Hospital, the treatment of these two complications seemed notably beneficial in the following ways: (1) early tracheotomy and insertion of a tube with inflatable muffs, (2) frequent suctions and bronchoscopies, (3) postural drainage, and (4) manual ventilation with balloon.

Such a conduct of the treatment has resulted in a reduction of the mortality rate, which fell from over 80% to under 40%, in the author's personal experience. He hopes this reduction will be still more marked in the future.

FROM THE AUTHOR'S SUMMARY.

A CASE OF POLIOMYELITIS IN A PREMATURE INFANT TWO MONTHS OLD. L. ROCCO, Lattante **24**:470 (July) 1953.

An 8-week-old baby, born one month premature and weighing 2,450 gm., developed fever, spinal fluid changes, and paralysis of the right arm. The paralysis had persisted until the child died of a respiratory infection some months later.

HIGGINS, Boston.

GAMMA GLOBULIN IN PROPHYLAXIS AGAINST MEASLES AND INFECTIOUS HEPATITIS IN CHILDREN. V. MIONE, Pediatria **61**:901 (Nov.) 1953.

Gamma globulin was given by injection to 25 children who had been exposed to measles in a pavillion of a tuberculosis sanatorium. Only one of these children developed measles, that child having an attenuated case lasting only one day.

This same institution was also troubled by an endemic of infectious jaundice; 61 children had had the disease, and one had died. One hundred seventy-eight out of 453 children were immunized by gamma globulin; two new cases of infectious jaundice appeared within two weeks from this group. Both cases were obviously attenuated; one of these two had also a mild recurrence some months later. No other cases had appeared in this group after four and one-half months; presumably the protection from the gamma globulin had lasted that long. Of the 275 children not receiving the gamma globulin, 12 had had attacks of infectious jaundice during this four and one-half month period.

HIGGINS, Boston.

UNUSUAL COMPLICATIONS IN A CASE OF MENINGOCOCCIC SEPTICEMIA. P. DE ANGELIS, Pediatria **61**:921 (Nov.) 1953.

A 10-year-old girl developed the purpuric type of meningococcic septicemia. Large doses of penicillin (20,000,000 units) were used without effect. On the third day, oxytetracycline (Terramycin) was given, and on the fifth day, the temperature fell to normal. Some of the purpuric areas became gangrenous and ulcerated. Other complications included a broncho-pneumonia, a polyserositis with pleuritic and pericardial effusions, paralyses of both legs and arms, and a glomerulonephritis with albuminuria and hematuria. The child recovered, the only residuals being a paralysis of muscles controlled by the left medial nerve and numerous scars.

HIGGINS, Boston.

A STUDY OF MEASLES. JAVIER MATOS AGUILAR and ENRIQUE CASADO DE FRIAS, Acta pediat. españ. **11**:281 (March) 1953.

The authors make a very extensive study of measles, giving the history, epidemiology, etc., as well as the complications which may prove serious to infants.

They discuss gamma globulin in prevention and treatment, and the use of penicillin in the complications.

ALLEN, Santa Fe, N. Mex.

THE COURSE OF VARICELLA IN CHILDREN ILL WITH INFECTIVE HEPATITIS. V. KREDBA, Pediat. listy **8**:200, 1953.

Attention is drawn to the atypical course of chicken pox in hepatitis. In 18 children with hepatitis, chicken pox took its course without temperature, with no catarrhal signs, and with only a faint rash. The rash resembled urticaria, in the form of papules with no typical vesicles. In four of the children who either had no hepatitis or had already gone through it, the chicken pox had an ordinary course.

FROM THE AUTHOR'S SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

SOME OBSERVATIONS ON UMBILICAL HERNIA IN INFANTS. GRACE E. WOODS, Arch. Dis. Childhood **28**:450-462 (Dec.) 1953.

Two hundred eighty-three infants with umbilical hernia have been studied.

Umbilical hernia is compatible with normal healthy growth, and its occurrence is, in part, dependent on the child's inherited status. Constitutional conditions causing either hypotonicity of the abdominal musculature or a rise in the intra-abdominal pressure favor the development of a hernia and aggravate the condition if present.

In infants, symptoms directly attributable to umbilical hernia are rare, and no case of strangulation has been recorded.

Spontaneous cure is a very common event. The use of restrictive appliances, such as strapping and trusses, frequently aggravate the condition and delay a spontaneous cure.

The ultimate incidence in school children and early adult life is very low.

KELLY, Milwaukee.

THE DIAGNOSIS AND TREATMENT OF EPIDEMIC DIARRHOEA. ALISON GARVEN, M. J. Australia **2**:447-450 (Sept. 19) 1953.

Epidemic diarrhea here refers to the common type of acute gastroenteritis of children, rather than that occurring in newborn nurseries.

Techniques of bacteriologic study are outlined. It is found that many cases are due to strains of Vacillus coli, paracolon bacilli, or virus etiology.

No treatment is presented.

McGUIGAN, Evanston, Ill.

ETIOLOGY, PATHOLOGY AND DIFFERENTIAL DIAGNOSIS OF CIRRHOSIS OF LIVER IN CHILDREN. A. V. SARMA, Indian J. Pediat. **20**:154-161 (July) 1953.

Cirrhosis in children is discussed rather haphazardly. Little is said of etiology or pathology in the paper itself, stress being laid on differential diagnosis. Diagnosis includes all the hepatomegalies, almost all the infectious tropical diseases, and various enteritides.

The author suggests an allergic diathesis as the basic element in the pathology of the disease, which is due to the switch-over period of the adrenal cortex rendering the liver vulnerable to cirrhosis. He feels that the clue to the pathology and therapy of cirrhosis may actually lie in the adrenal cortex.

McGUIGAN, Evanston, Ill.

LARGE ABDOMINAL SWELLINGS IN CHILDHOOD. J. J. LOUW, South African M. J. **27**:1020-1026 (Nov. 14) 1953.

Twenty-eight children under 11 years of age, with large abdominal symptomless swellings, are discussed. The tumors were found in every quadrant of the abdomen, in the abdominal wall, intraperitoneally, and retroperitoneally. The majority, 16, were found in the flanks and were extraperitoneal, apparently arising from the kidneys. Thirteen of these actually were found to arise from the urinary system.

There were 9 congenital cases, 4 inflammatory, 13 neoplastic, and 2 of hydatid disease. Congenital cases included six urinary system anomalies, a retroperitoneal cyst, and a choledochal cyst. The four inflammatory cases were low-grade abscesses, two of them retroperitoneal.

All swellings in infants under the age of 3 months were congenital anomalies. Three of every four cases in children 11 months to 5 years were malignant neoplasms. In children 6 to 10 years, no malignancies were found, and most of the swellings were benign cysts.

Malignancy was present in 10% of the 28 cases, all occurring under the age of 6 years. Eight of the 16 retroperitoneal swellings were malignant, and 7 of them were of renal origin.

McGUIGAN, Evanston, Ill.

PERIODIC ABDOMINAL PAIN. H. ZELLWEGER and H. A. REIMANN, Helvet. paediat. acta **8**:377 (Nov.) 1953.

A typical case of periodic abdominalgia is presented. This disease occurs quite frequently in Lebanon, mainly among Armenians. The clinical picture of the acute attack is similar to that of an acute peritonitis, however, the periodicity of the disease differentiates it from the so-called acute surgical abdomen. During the acute attacks, a serofibrinous exudate in the abdominal cavity and acute periappendicitis is found. Yet these pathological findings are so mild that their responsibilty for the severe clinical picture cannot be stated. The etiology and pathophysiology of the disease is unknown. In a few instances, a relation to epilepsy may exist, and a case of periodic abdominalgia and epilepsy is described.

FROM THE AUTHORS' SUMMARY.

APPENDICITIS OR PSEUDOAPPENDICITIS IN THE CHILD? W. TANGERONI, Minerva pediat. **5**:1104 (Dec. 15) 1953.

Two children with paratyphoid fever had abdominal distentions and pain and tenderness in the right lower quadrant. Appendectomy was considered, but not done. It is likely there was some localization of the paratyphoid infection in the ileocecal region. X-ray films taken one month after recovery showed no abnormal shadows in this area.

HIGGINS, Boston.

Nervous Diseases

BILATERAL ENCAPSULATED SUBDURAL EFFUSION COMPLICATING BACTERIAL MENINGITIS IN INFANCY. J. EPSTEIN and SANFORD GOLDZIER II, A. M. A. Arch. Neurol. & Psychiat. **69**:242-249 (Feb.) 1953.

Review of the literature following a case of subdural effusion revealed 39 cases following various forms of bacterial meningitis. This complication has occurred only since the advent of antibiotic and chemotherapeutic measures.

McGUIGAN, Evanston, Ill.

COMMON NEUROSURGICAL PROBLEMS IN GENERAL PRACTICE. HAROLD C. VORIS, Illinois M. J. **103**:33-36 (Jan.) 1953.

This presentation deals with five symptom complexes frequently met with which may indicate the presence of a neurological condition.

Headaches (continual or recurrent).—From a neurologic standpoint, the most important diagnostic categories to consider are cerebrovascular anomalies or disease, migraine, post-traumatic states, increased intracranial pressure, and psychogenic headaches.

Epilepsy.—Patients with epilepsy can be classified as those whose seizures have an organic cause in some demonstrable disease or injury of the brain and those of the so-called idiopathic group. The usual clinical classification of convulsive seizures divides them into grand mal, Jacksonian seizures, petit mal, and so-called psychomotor seizures. It is the Jacksonian seizures which are most often caused by a local irritative lesion. They usually have an organic cause and can be localized by the location of the seizure. The age of onset of the seizures furnishes some presumptive clue to their cause.

Sciatica.—This syndrome must be considered a symptom, not a disease, and a thorough search needs be made for the cause. It may be produced by neurologic, skeletal, or muscular involvement.

Intractable Pain.—For the purpose of his discussion of this symptom complex, Voris describes intractable pain as pain constant and severe enough to require the continued use of narcotics for relief and either due to inoperable malignant disease or to some other condition not amenable to direct treatment. These conditions are enumerated and discussed.

Hydrocephalus.—Since any expanding intracranial lesion in the infant will produce enlargement of the head, Voris believes that every such case should have a diagnostic bilateral subdural tap in order to rule out subdural hematomas, neoplasms, or even abscesses. Then, if these conditions are not found, dye and air studies should be made to determine whether a block in the ventricular system exists, to determine the type and location of the causative lesion, and for evaluating the degree of enlargement of the ventricles and consequent cerebral damage. If feasible, a direct attack should be made on the cause of the obstruction. If this is not feasible, there are a variety of palliative surgical procedures which Voris describes either for shunting the flow of cerebrospinal fluid around the obstruction or for drainage of the fluid into some other body cavity.

BARBOUR, Peoria, Ill.

RECOGNITION OF SURGICALLY TREATABLE NEUROLOGICAL DISORDERS OF CHILDHOOD. JONATHAN M. WILLIAMS and HAROLD STEVENS, J. A. M. A. **151**:455 (Feb. 7) 1953.

After repair of a meningocele, the development of the Arnold-Chiari malformation causing hydrocephalus has to be corrected by resection of the cerebellar tonsils.

Idiopathic scoliosis is often caused by a spinal cord tumor.

Pott's disease of the spine may interfere with the blood supply of the cord, therefore the neurological correction of this difficulty is more important than correcting the skeletal structure. The bones can wait but the nervous system cannot.

Astrocytomas can be removed. Depressed bone in a fracture can be elevated. A brain abscess can be drained. Many surgical treatments can be used in tuberculous meningitis. Subdural effusions should be looked for in meningeal infections that are not doing well.

KIMBALL, Evanston, Ill.

HYDROCEPHALUS TREATED BY ARACHNOID-URETEROSTOMY. DONALD D. MATSON, Pediatrics **12**:326 (Sept.) 1953.

Parents of an infant with hydrocephalus are interested not just in having their child kept alive, but in giving it a chance for normal development. Therefore, once it is established that progressive hydrocephalus exists, temporizing measures and prolonged observation should be discouraged in favor of a definitive procedure which will immediately and continuously reduce spinal fluid pressure to within normal limits. This series of patients indicates that this objective can be accomplished by diversion of cerebrospinal fluid into the urinary tract. The complications of this procedure are three: (1) mechanical obstruction of the shunt, which has been seen in only a few cases and has always been remediable; (2) meningitis, which has occurred in 8 out of 50 patients postoperatively and has been fatal in three, and (3) acute dehydration secondary to intercurrent infection because of unreplaced loss of fluid and electrolytes through the shunt, which has been fatal in 8 to 10 of these patients.

Thirty-three out of 50 patients with severe communicating hydrocephalus treated by arachnoid-ureterostomy are living, and of these, 31 are satisfactory to excellent results to date. At least 24 of these children appear to be entirely asymptomatic with normal or close to normal mental and physical development at periods from a few months to over four years.

FROM THE AUTHOR'S SUMMARY.

THE ATAXIC CHILD. J. K. MARTIN, Canad. M. A. J. **69**:601-606 (Dec.) 1953.

Attention is called to the ease with which ataxia may be missed during routine examination unless the child is made to walk.

Ataxia in children is most commonly cerebellar in origin. Case reports are included to illustrate the classifications of congenital, acute, and progressive ataxia.

McGUIGAN, Evanston, Ill.

ETIOLOGY, MANAGEMENT AND PSYCHOLOGICAL TREATMENT OF THE CONVULSIVE DISORDERS IN YOUNG CHILDREN. H. N. DAVY, Great Ormond St. J. (No. 5) pp. 27-39, June, 1953.

The author advocates a biological concept of convulsive seizures—the "epilepsies" and allied behavior disorders—because it influences the attitude toward treatment. Five etiological factors are suggested in this concept: heredity, brain injury, physiological disturbances, personality maladjustment, and environmental fault. By such an approach, treatment includes not only increasing the anticonvulsant threshold but also treating the child's social and emotional handicaps. The possibility of preventing secondary personality maladjustment is stressed. The combined knowledge of the family physician, neurologist, neurosurgeon, electroencephalographer, and pediatrician can help to clarify diagnosis and treatment.

McGUIGAN, Evanston, Ill.

MENINGITIS IN CHILDHOOD. B. K. CHAUDHURI, Indian J. Pediat. **20**:15-24 (Jan.) 1953.

Sixty cases of meningitis observed between April, 1950, and April, 1952, are analyzed. Cases were divided into purulent and nonpurulent (tuberculous meningitis).

The author notes that the incidence of meningitis has not lessened despite the antibiotics and sulfonamides, and that tuberculous meningitis has increased.

Complications included severe convulsions in 8 cases, hyperpyrexia in 10, Cheyne-Stokes respiration, very common, especially in tuberculous cases, and sudden death in 4 cases of tuberculous meningitis. Sequelae included three cases of hydrocephalus, one of blindness (influenzal meningitis), and one of generalized spasticity.

Age incidence showed purulent meningitis most common in 7- to 8-month-old infants, tuberculosis in 1- to 1½-year-old infants. Mortality rates were 100% in tuberculous meningitis and 43.5% in purulent meningitis.

McGUIGAN, Evanston, Ill.

THE SYNDROME OF MELKERSON-ROSENTHAL. K. MEYER, Ann. pædiat. **180**:111 (Feb.) 1953.

The author reports a case of the Melkerson-Rosenthal triad in a boy 14 years of age, with recurring edema of the face, facial paresis, and lingua plicata. There are doubtless connections

between the facial paresis and the edema, while the folded tongue belongs to the syndrome only as a constitutional sign. Inflammatory processes and focal infections in the nasopharynx, as well as allergic reactions, have to be considered as pathogenetic causes. The difficult detection of the sole responsible factor necessitates purely symptomatic treatment.

FROM THE AUTHOR'S SUMMARY.

PNEUMOCOCCIC ENCEPHALITIS. R. GOLDSTEIN, Ann. pædiat. **180**:118 (Feb.) 1953.

This is a report on two children with pneumococcal meningitis who were treated exclusively with very large intramuscular doses of penicillin. In spite of this, encephalitic symptoms were observed, but both children were completely cured. It is assumed that the brain substance becomes sensitized by the pneumococcal meningitis and that a state of neuroallergic encephalism can be produced either by bacterial toxins, by morbid substances, or by the penicillin.

FROM THE AUTHOR'S SUMMARY.

HYDRANENCEPHALY DIAGNOSED IN VIVO. E. NAJMAN, Ann. pædiat. **181**:249 (Oct.) 1953.

In a 2-month-old baby girl disturbances of sucking and swallowing were present since birth. The child did not develop satisfactorily and was admitted to hospital.

Disturbances of sucking and swallowing, hypothermia, spasticity, and bradycardia indicated a defect of the central nervous system. The circumference of the head was normal. Transillumination of the head made the diagnosis of hydranencephaly highly probable. The value of transillumination of the head for the diagnosis of large defects of the brain is emphasized.

FROM THE AUTHOR'S SUMMARY.

A CASE OF ACUTE MENINGITIS DUE TO MORAXELLA LACUNATA. M. PAVLATOU and T. ATHANASIADES, Helvet paediat. acta **8**:104 (March) 1953.

A case of purulent menigitis due to Moraxella lacunata is reported in a 4-month-old infant boy. Moraxella lacunata was isolated from the blood, bone-marrow, and spinal fluid in pure culture. Prompt recovery followed penicillin and sulfamethazine therapy.

FROM THE AUTHORS' SUMMARY.

CHRONIC HYPOCALCEMIA AND TETANY OF CEREBRAL ORIGIN. T. NEUHAUS, H. ZELLWEGER, and G. FANCONI, Helvet. paediat. acta **8**:237 (June) 1953.

A case is reported showing severe hypocalcemic tetanic convulsions during the first four months of life. Myoclonic contractions of the face and clonic contractions of the extremities appeared at the same time. Finally typical "Nick and Saalam" seizures were seen. The high-grade hypocalcemia was accompanied by normal phosphate and phosphatase levels. There was evidence of increasing congenital internal and external hydrocephalus. The child died at 16 months of age. Autopsy showed a hypoplasia of the neocerebellar structures and dependent formations, as well as a malformation of the fornix.

It was concluded that the hypocalcemia and the tetany were of cerebral origin.

FROM THE AUTHORS' SUMMARY.

POSSIBLE RELATIONSHIP BETWEEN HYDROCEPHALUS AND RICKETS. ANIELLO MACCIOTTA, Ann. ital. pediat. **6**:55 (Feb.) 1953.

The author examined the association between rachitism and hydrocephalus, reporting that it was seen in 26.1% of hydrocephalus and in 20% of rachitics.

He fixes the clinical, radiological, and metabolic aspects and then discusses the connections of interdependence. He thinks we must exclude in them a dependence of rachitis process on hydrocephalic process and that it may rather be that the former creates a favorable condition for the latter.

FROM THE AUTHOR'S SUMMARY.

THE EFFECT OF THE INTRATHECAL INJECTION OF FIBRINOLYTIC AND PYOLYTIC ENZYMES IN HIGH CONCENTRATION ON THE SPINAL FLUID, THE MENINGES, AND THE BRAIN. E. CHELI, Clin. pediat. **35**:315 (May) 1953.

Certain fibrolytic and/or pyolytic enzymes—Varidase (streptokinase-streptodornase), and Fibrinoclasi and Colliquasi (Istituto Farmacologico Sereno)—were injected in high concentration into the cerebrospinal fluid of rabbits by cisternal puncture. No untoward symptoms or pathological injury resulted. These preparations may have clinical value in preventing spinal fluid blocks in patients with meningitis, especially tuberculous meningitis. HIGGINS, Boston.

THE CLINICAL SYNDROME "ENCEPHALOMYOCARDITIS." KLAUS BETKE and INGRID HARMS, Arch. Kinderh. **146**:6-16, 1953.

The authors present a discussion of the literature on virus encephalitis and poliomyelitis associated with myocarditis. Description is given of a virus epidemic in the southern part of Baden. Eleven cases are discussed in detail. Seven occurred in infants, two in children of preschool age, two in children of 12 years. Most cases were in larger communities, in close proximity to traffic, in two cases there was simultaneous family grippal diseases, and in two cases probably postvaccinal encephalitis. The signs were unconsciousness, convulsions, pareses, fundus changes, extrapyramidal manifestations, and increase of sugar in liquor. The myocardial signs were A-V block, ventricular extrasystoles, and prolongation of Q-T. The prognosis was guarded. Some cases showed complete recovery, in others permanent damage of the basal ganglia, hemiparesis, or hydrocephalus persisted. Since a virus was the probable etiological factor, broad-spectrum antibiotics were administered. GOTTSTEIN, Chicago.

SUBARACHNOID HEMORRHAGE IN CHILDHOOD. DIETER EBEL, Monatsschr. Kinderh. **101**:275-277 (May) 1953.

A 13-year-old boy suddenly collapsed, with abdominal cramps and vomiting. After consciousness returned, he developed fever, severe headaches, psychological changes, and paralysis of the hypoglossal nerve. Lumbar puncture revealed grossly bloody fluid without evidence of inflammation. A diagnosis of acute subarachnoid hemorrhage due to aneurysm rupture (meningeal apoplexy) was made and later confirmed by arteriography and exploratory craniotomy. These revealed a saccular aneurysm of the anterior cerebral artery just after it came off the internal carotid artery. At surgery, a piece of muscle was placed around the aneurysm, as direct repair was impossible.

The patient recovered completely after three months except for minimal weakness of the hypoglossal nerve and has remained in good health for one year.

Differential diagnosis should include other vessel abnormalities besides aneurysm, tumors, pachymeningiosis, hemorrhagic diathesis, meningitis, hemorrhagic encephalitis, malignant nephrosclerosis with cerebral apoplexy, diabetic or uremic coma, cerebral complications of infectious diseases, poisonings, and, rarely, trauma.

Cerebral aneurysm is due to dilatation of a congenitally weak portion of a blood vessel. Prognosis in childhood is more favorable than in adults.

HARTENSTEIN, Syracuse, N. Y.

ACUTE DIFFUSE INFANTILE SCLEROSIS OF THE BRAIN (KRABBE'S DISEASE): A REPORT ON TWO CASES IN SIBS. ARNE KASS, Acta pædiat. **42**:70 (Jan.) 1953.

The heredofamilial degenerative diseases of the central nervous system are briefly reviewed, and an account is given of two cases of acute diffuse infantile sclerosis of the brain in a brother and sister. In both cases a typical picture developed from the fifth to the sixth months of life, and death occurred after the disease had lasted about 10 months. The family history yielded no data concerning diseases of the nervous system or the like, and the disease is taken to be the outcome of a recessive hereditary process. FROM THE AUTHOR'S SUMMARY.

Psychology and Psychiatry

THE IMPORTANCE OF CONSTITUTION IN PSYCHIATRY. G. LANGFELDT, Am. J. Psychiat. **110**:261 (Oct.) 1953.

In this paper the term "constitution" implies "the total psychobiological outfit of an individual so fixed that it can scarcely be changed except by longlasting psychical or physical influences." The existence of well-defined types of constitutions that play an important part in pathology and criminology is well supported by investigations in heredity as well as by clinical investigation.

According to Langfeldt, in clinical psychiatry one sees the sensitive type, the cyclothymic and schizoid, the hysterical, the compulsive, the paranoic, and the paranoid. The fundamental and central traits in all these character types are of hereditary origin, and psychotherapy, even at an early age, does little to change these character types, with the exception (perhaps) of the hysterical and the paranoic.

The description of each of the constitutional types mentioned and a digest of the author's philosophy is worthy of attention of every pediatrician interested in total child development as it pertains to parental guidance.

JAHR, Omaha, Neb.

A BALANCED CONCEPT OF CHILD TRAINING WITH SOCIAL IMPLICATIONS. FREDERIK T. ZIMMERMAN and BESSIE B. BURGEMEISTER, Am. J. Psychiat. **110**:143 (Aug.) 1953.

This is a most valuable comprehensive discussion of the problem of child training, with particular emphasis on the mentally retarded child. The authors justly decry the results of mismanagement so frequently encountered in this area of pediatric practice. Faulty diagnosis, pessimistic attitudes, and poor counsel lead to parental discouragement and family confusion, ending in overprotection and rejection of the child.

Methods of diagnosis, therapy, and guidance are described which, in the author's experiences, have proved beneficial to patient and family alike.

This paper should be read in the original by every pediatrician.

JAHR, Omaha, Neb.

LEVEL OF ACHIEVEMENT AFTER LOBOTOMY: A STUDY OF ONE THOUSAND CASES. WALTER FREEMAN, Am. J. Psychiat. **110**:269 (Oct.) 1953.

An analysis of over 1,000 lobotomized patients followed over a period of 1 to 16 years is presented from the standpoint of social achievement. A good deal of misunderstanding regarding the purpose of prefrontal lobotomy and too many misgivings on the results of the procedure exist largely because of scarcity of reliable evaluation of patients on whom the operation had been performed and also because too often data accepted as final only represent short-term follow-up. Ir his studies, Freeman found improvement in some cases occurring five years postoperatively.

Patients in this report include 622 who were subjected to the Freeman-Watts procedure and 498 who underwent transorbital lobotomy. Results are presented graphically, depicting the adjustment levels in the individual etiological categories for which the operations had been performed as well as the factors involved in influencing good or poor achievement at various social levels.

The author concludes that, "Since community activities and professional competence are possible after lobotomy, it is apparent that personality downgrading generally attributed to lobotomy should be attributed rather to the devastating effects of the underlying disease process."

JAHR, Omaha, Neb.

THE CONTRIBUTION OF THE FATHER TO THE MENTAL HEALTH OF THE FAMILY. LES BARTEMEIER, Am. J. Psychiat. **110**:277 (Oct.) 1953.

This is a brief discussion of the paternal influences in the social and emotional development of the children in the family. The author suggests that the purposes and services of the Cornelius Corner could be properly enhanced by its inclusion of fathers in its circles of study.

JAHR, Omaha, Neb.

THE EFFECT OF INFANTILE DISEASE ON EGO PATTERNS. ROY R. GRINKER, Am. J. Psychiat. **110**:290 (Oct.) 1953.

The adverse influences of prolonged illness on the development of the ego are profound and assert themselves long after physical recovery. This the author attributes to the fact that during the first few months of life soma and psyche are undifferentiated. To illustrate the point, Grinker presents the case of a patient who for the first eight years had suffered from celiac disease. An adult of college age, now under analytic therapy, this patient expresses in symbolic form his early behavior pattern referable to symptoms of the disease. Hunger constitutes a sudden awareness of a need to study and learn. Greedy eating expresses itself periodically in an effort to devour work assignments. Slow assimilation is portrayed by anxiety over his difficulty in understanding mathematical problems thoroughly and quickly. Expulsion expresses itself in recounting with great ceremony what he had learned, even though the listener may show no interest in the patient's distention with knowledge.

JAHR, Omaha, Neb.

THE EFFECTS OF A MOTOR HANDICAP ON PERSONALITY: I. THE EFFECTS ON LEVEL OF ASPIRATION. CHARLES WENAR, Child Developm. **24**:123 (June) 1953.

In order to determine the effect of a motor handicap on setting goals of achievement, 12 nonhandicapped, 12 moderately handicapped, and 12 severely handicapped children were given a level-of-aspiration task involving five trials of putting pegs in a pegboard. There was no significant tendency for the handicapped groups to set higher or lower goals for themselves when all five trials were combined. However, there was a significant change in pattern of goal-setting from trial to trial, the nonhandicapped group progressively lowered their level of aspiration, in contrast to an initial lowering followed by a reversal toward setting higher goals as the task was continued on the part of the handicapped groups. This was interpreted as meaning that, when faced with a motor task, the handicapped child can maintain a realistic attitude toward his capabilities for only a limited period of time; then, under the pressure of the frustrations of limited or unpredictable achievement, his attitude changes to a wishful one of what he would like to be able to do rather than what he is capable of doing.

FROM THE AUTHOR'S SUMMARY.

USE OF MOTION PICTURES IN EFFECTING GROUP ADJUSTMENT CHANGES IN SPEECH HANDICAPPED ADOLESCENTS. D. E. MORLEY and STANLEY BERLINSKY, J. Speech & Hearing Disorders **18**:38-42 (March) 1953.

A student group between the ages of 12 and 19 years, enrolled in the University of Michigan speech clinic, was studied on the Bell Adjustment Inventory before and after a series of motion pictures especially related to personality and social adjustment. No differences were found in the areas of home, health, and emotional adjustment. Statistically significant differences occurred in the area of social adjustment.

PALMER, Wichita, Kan.

BEHAVIOUR PROBLEMS IN CHILDREN. PAUL WILLIAMSON, Canad. M. A. J. **69**:412-415 (Oct. 6-9) 1953.

Some of the common behavior problems of childhood are briefly discussed, including lying, fear, stealing, and temper, obedience, and jealousy. The author quotes Holt to the effect that rewards are much more effective than punishment, a fact more generally appreciated by animal trainers than by parents.

MCGUIGAN, Evanston, Ill.

CROSSED LATERALITY: A STUDY IN ITS SIGNIFICANCE AND TREATMENT IN ORDINARY SCHOOL LIFE. ROBERT A. H. PEARCE, Arch. Dis. Childhood **28**:247-258 (Aug.) 1953.

Crossed laterality was found among children in a boarding school. Its prevalence and etiology are examined.

The natural history and symptomatology are related to observed educational problems.

Experiments are described whose aim has been to discover the mechanism whereby the symptoms arise.

Effective treatment, which has been suggested by observation of the natural history of the condition and of experimental findings, is recorded.

KELLY, Milwaukee.

PSYCHOPATHY IN CHILDHOOD. G. KRAUS, Maandschr. kindergeneesk. **21**:1 (Jan.) 1953.

There is a gradually growing insight with regard to the importance of environmental factors which can bring about psychopathic states, especially in early youth and in persons who have a hereditary taint. It is above all the pediatrician who has the opportunity to observe personality changes in young children and who can eventually do valuable preventive work in this field. The author reviews the psychological environmental influences, such as neglect and deprivation of maternal love and the physical factors acting before, during, and shortly after birth which can play their part in the causation of the development of psychopathic states.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

DEVELOPMENTAL DEFECTS FOLLOWING IRRADIATION OF THE OVARIES IN A CHILD. U. V. PORTMANN and E. PERRY MCCULLAGH, J. A. M. A. **151**:737 (Feb. 28) 1953.

At the age of 2 years, a pelvic neuroblastoma was irradiated. At 18 years of age, breasts and pelvis were still child-like, without menstruation. However, there was no evidence of an ovarian tumor. Diethylstilbestrol and progesterone were used to stimulate the breasts and artificially produce menstruation.

KIMBALL, Evanston, Ill.

OBSERVATIONS OVER A FIVE-YEAR PERIOD OF A PATIENT WITH NEPHRITIS TREATED WITH SEVENTY-ONE INFUSIONS OF TEN PER CENT GELATIN SOLUTION. RAY VANDERMEER, J. Pediat. **42**:339 (March) 1953.

The author used a gelatin with a mean molecular weight of 45,000. It was given in a 10% solution. It was diuretic and produced no untoward side-effects.

MACDONALD, Pittsburgh.

TRUE HERMAPHRODITISM. FRANKLIN R. SMITH, Northwest Med. **52**:1022 (Dec.) 1953.

The author presents a review of all of the cases of true hermaphroditism, proved by microscopic demonstration of both ovarian and testicular tissue. To date there are 47 cases, including the author's.

He discusses the management of the patient preferring to be a man and the management of the patient preferring to be a woman. A great deal of attention is given to the surgical procedures and techniques necessary to emphasize these preferences and minimize or eliminate the manifestations of the undesired sex. This is a simple concise review of a most complicated subject.

DOCTER, Seattle.

OVARION MATURATION AND CYST FORMATION IN CHILDREN. DONALD W. POLHEMUS, Pediatrics **11**:588 (June) 1953.

The results of study of a number of ovaries removed from infants and children at autopsy are presented. Follicle maturation and cyst formation were found to be extensive, even in earliest infancy. The relationship of these findings to present knowledge and current theories regarding histogenesis of cysts is discussed.

FROM THE AUTHOR'S SUMMARY.

E.E.G. FINDINGS IN ONE HUNDRED CASES OF SEVERE ENURESIS. E. C. TURTON and A. B. SPEAR, Arch. Dis. Childhood **28**:316-320 (Aug.) 1953.

The E.E.G's from 100 cases of severe enuresis without any organic condition were studied in detail.

Only 26 of these were completely normal, and a further 23 were on the borderlines of normalcy.

Of the abnormal records, 28 showed a too slow or immature type of record. A further one showed an organic type of tracing.

The remainder, 22 in all, were of an epileptiform type, with 14 of these showing typical seizure patterns either at rest or during activation procedures.

KELLY, Milwaukee.

A Case of Calcium Oxalate Nephrocalcinosis. G. H. Newns and J. A. Black, Great Ormond St. J. (No. 5) pp. 40-44, June, 1953.

A case of calcium oxalate nephrocalcinosis in a 2½-year-old girl is described. One brother had died at 8½ years from the same disease, and a great-uncle had suffered from renal calculi. Detailed chemistry studies are included, and possible theories as to cause are discussed. In this case there was excessive excretion of oxalic acid.

McGuigan, Evanston, Ill.

A Case of Prostatic Abscess in Early Infancy. Phyllis A. George, Great Ormond St. J. (No. 5) pp. 58-60, June, 1953.

An infant 5 weeks old, with an abscess in the scrotum, was found to be suffering with a prostatic abscess which was the primary infection. Drainage and antibiotics resulted in cure.

McGuigan, Evanston, Ill.

Renal Calculus in Children. Giovanni Canestri, Riv. clin. pediat. **51**:490 (Dec.) 1953.

The author examines the cases (two) of renal calculus in the childhood seen in the Children's Hospital of Alessandria from 1942 to 1952. He points out the present rarity of such affection, then he discusses the etiopathogenesis outlining the great importance of hyperparathyroidism, as the calculus of the two mentioned cases are constituted of calcium compounds. He calls attention to the diversity of the symptoms and therefore of the diagnostic difficulty.

From the Author's Summary.

Diseases of Ductless Glands; Endocrinology

The Effect of Hypophysectomy on the Regeneration of the Liver After Partial Hepatectomy in Dogs. Talib M. Astarabadi, Hiram E. Essex, and John H. Grindlay, Endocrinology **52**:652 (June) 1953.

Regeneration of the remaining portion of the liver after partial hepatectomy in the dog is rapid and complete within five to eight weeks.

The effect of hypophysectomy on regeneration of the liver after partial hepatectomy in dogs was studied, and it has been found that the absence of the hypophysis cerebri does not seem to interfere with regeneration of the liver.

Severe and sometimes fatal hypoglycemia developed in a few of the completely hypophysectomized dogs after fasting. It was hastened and aggravated by partial removal of the liver.

Jacobsen, Buffalo.

Electron Microscopic Observations on the Thyroid. H. Braunsteiner, K. Fellinger, and F. Pakesch, Endocrinology **53**:123 (Aug.) 1953.

Using an electron microscope, a submicroscopic canalicular structure of the cytoplasm could be demonstrated in the follicular cells. The appearance of this structure seems related to the functional state of the gland. The cells show fine intrafollicular projections that seem augmented during reabsorption of liquefied colloid.

Jacobsen, Buffalo.

Effect of Pancreatic Extracts on Ketone Body Production of Rat Liver. Ronald D. Stewart and Ellen Roitman, Endocrinology **53**:192 (Aug.) 1953.

The results of these experiments show that it is possible to prepare insulin-free pancreatic extracts which cause hyperglycemia on intravenous injection and depress the rate of ketone-body production by the liver.

Jacobsen, Buffalo.

Diabetes in Childhood. Edwin L. Rippy, J. Louisiana M. Soc. **105**:421-426 (Nov.) 1953.

The author uses a method of control in patients with recently discovered diabetes involving three periods. The first, which lasts about a week, includes establishment of diet and insulin to overcome glycosuria and ketonuria; the second, lasting two and three weeks, covers a period

of metabolic recovery, where improvement is rapid and insulin dosage can be induced. Lastly, is the period of stabilization, lasting two to three weeks, wherein the insulin requirement becomes relatively constant.

Food requirements are outlined: 1,000 Cal. per day and 100 for each year of age; 2 gm. per pound (0.5 kg.) of body weight of protein, or about 20% of total calories; 40% of total calories in carbohydrates; fats in amount needed to complete caloric need.

NPH insulin is recommended after control is reached. Unmodified insulin is used "on demand," while establishing control. Hypoglycemia is to be avoided in children. The author feels that there is no place in childhood diabetes for the so-called free diet, though perfect control is probably possible.

McGUIGAN, Evanston, Ill.

DIABETES INSIPIDUS IN INFANCY RESISTANT TO PITRESSIN. MARY YUN-CHEN KAO and MATTHEW M. STEINER, Pediatrics **12**:400 (Oct.) 1953.

The authors have presented the report of a 6½-month-old Negro boy who, shortly after birth, developed polyuria, polydipsia, fever, vomiting, dehydration, constipation, and failure to gain weight.

Investigations ruled out systemic infections, as well as the common inflammatory and congenital renal diseases.

Under "control" conditions (average fluid intake) there was a persistence of the fever, vomiting, and constipation; the values for nonprotein nitrogen and serum sodium and chloride were elevated above normal. The polyuria, which was characterized by low specific gravity, rose to a value of 1.011 during periods of marked dehydration.

During the "hydration test," a progressive increase of fluid intake above 2,000 cc. daily resulted in normal temperature, absence of vomiting, increase of weight, and normal values for nonprotein nitrogen and serum sodium and chloride.

There was no antidiuretic response to either intravenous infusion of hypertonic saline (Carter-Robbins' test) or to 0.1 unit of vasopressin (Pitressin) administered intravenously. A normal control showed prompt antidiuresis during and following the infusion of hypertonic saline.

Intramuscular administration of vasopressin to the point of toxicity (4 units) had no effect on the volume or specific gravity of the urine.

It is postulated that this syndrome of diabetes insipidus in infancy, resistant to vasopressin tannate, is the result of a failure of end-organ response in the kidney.

FROM THE AUTHORS' SUMMARY.

A CASE OF IDIOPATHIC HYPOPARATHYROIDISM. KENNETH SIMPSON, Great Ormond St. J. (No. 5) pp. 54-57, June, 1953.

A 5½-year-old boy with a history of epileptic fits, bilateral cataracts, and tetany, was found to have hypoparathyroidism. Good results were obtained with dihydrotachysterol. Cataracts and cerebral calcifications are not affected by restoration of normal blood levels.

McGUIGAN, Evanston, Ill.

DIABETES, PRE DIABETES, MOTHERS AND BABIES. W. P. W. JACKSON, South African M. J. **27**:795-797 (Sept. 12) 1953.

The author discusses the meaning of the "prediabetic state" and remarks that its only evident manifestation is the production of large babies and stillbirths in a woman who later develops overt diabetes. It is emphasized that glycosuria is not always present in pregnancy in such patients. A single high two- or two-and-one-half-hour reading is considered significant. These observations have been closely connected with large babies and stillbirths.

McGUIGAN, Evanston, Ill.

FURTHER PROGRESS ON A CASE OF PREMATURE VIRILIZATION. A. JESUS MARTINEZ FERNANDEZ, Acta pediat. españ. **11**:1023 (Nov.) 1953.

This is a further report on a boy 27 months of age with premature development of the muscles, advanced bone age, and precocious sex development, with elevation of the 17-keto-

steroids in the urine, but with no evidence of ejaculations or unusual sex interest. Full details of his advanced bone age and photographs are included.

The treatment has been largely expectant. However, thyroid and folliculin were given, with a ketogenic diet rich in carbohydrates but poor in sodium and protein, since the experimental work indicates that this type of diet reduces the production of cortical hormones.

Although there has been no evidence of suprarenal tumor, surgical intervention will be done should indications for it develop. In the meantime, psychological assistance is being given to the parents to keep the boy from developing abnormal behavior.

The first report was in this journal in May, 1953.

ALLEN, Santa Fe, N. Mex.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

SUBACUTE AND CHRONIC OSTEOMYELITIS: TREATMENT WITH USE OF CHEMOTHERAPEUTIC AGENTS, ANTIBIOTICS, AND PRIMARY CLOSURE; FOLLOW-UP REPORT. FRANK R. DICKSON, REX L. DIVELEY, and RICHARD H. KIENE, A. M. A. Arch. Surg. **66**:60 (Jan.) 1953.

Experiences with 104 cases of subacute and chronic osteomyelitis (23 cases from 0 to 10 years of age, 34 cases, 11 to 20) are reported. A total of 140 débridements and primary closures were carried out, 83.5% of the cases healing by primary intention. The authors stress injection of the draining sinus with methylene blue, the use of sulfathiazole locally and penicillin systemically, and the administration of Staphlyococcus toxoid to prevent recurrences, when indicated.

YANKAUER, Albany, N. Y.

PIGEON BREAST (PECTUS CARINATUM) AND OTHER PROTRUSION DEFORMITIES OF THE CHEST OF DEVELOPMENTAL ORIGIN. CHARLES W. LESTER, Ann. Surg. **137**:482-489 (April) 1953.

Protrusion deformities of the chest of congenital or developmental origin fall into two main groups: the midline protrusion, or pigeon breast, deformities and those in which the protrusion is unilateral and parallel to the sternum.

An explanation of the etiology of protrusion deformaties is offered which predicates an unequal growth of the ribs and the variation in the size and shape of the diaphragm.

The symptoms may be vague and concern poor physical development and easy fatigability; but definite dyspnea and chronic cough have been noted. Psychological disturbances due to the deformity are usually prominent.

Surgical procedures are described which can be used to correct these deformities.

BANTIN, Omaha.

STUDIES IN DISORDERS OF MUSCLE: SITE OF CREATINE SYNTHESIS IN THE HUMAN. A. E. SANDBERG, H. H. HECHT, and F. H. TYLER, Metabolism **2**:22 (Jan.) 1953.

The disturbance of creatine metabolism in disorders of muscle prompted an investigation of the site of synthesis of creatine in the human. This was accomplished by determining the concentrations of creatine and creatinine and two of their precursors, arginine and glycocyamine in hepatic and renal venous blood as well as in arterial blood. Samples of hepatic and renal venous blood were obtained by retrograde venous catheterization. The study indicated that the liver is the major site of creatine synthesis in the human.

KAPLAN, Cincinnati.

FUNNEL CHEST: INDICATIONS FOR SURGERY AND THE TIME OF CHOICE FOR SURGERY. ALEXANDER H. BILL JR., Pediatrics **11**:582 (June) 1953.

Funnel chest as seen in childhood very seldom produces disability.

A review of the literature reveals a growing number of cases of funnel chest in adult patients in whom varying degrees of cardiac disability have been described.

In a questionnaire answered by 25 American physicians, the majority felt that among adult patients with severe funnel chest there are some who suffer from cardiac or respiratory disability. There was a feeling that many of these patients undergo psychologic trauma.

Twenty-three of the 25 felt that operative correction of a severe degree of funnel chest should be undertaken in childhood.

A series of eight cases operated upon by the author is reviewed. Of these cases, the outcome has been the most successful in children operated upon by radical surgery between 2 and 6 years of age.

The author believes that for children with a severe grade of funnel chest, surgery should be recommended when they are between 2 and 6 years of age.

FROM THE AUTHOR'S SUMMARY.

A CASE OF OSTEOMYELITIS OF ALL THE SMALL BONES OF THE HANDS AND FEET. M. D. BABER, Arch. Dis. Childhood **28**:25 (Feb.) 1953.

A case of osteomyelitis involving all the small bones of hands and feet and one ulna in a child of 15 months is described. No similar case has been found in a search of the literature. With prolonged penicillin therapy and without recourse to surgery, the patient recovered completely.

KELLY, Milwaukee.

ON OUR KNOWLEDGE OF CHONDRODYSPLASIA CALCIFICANS CONGENITA AND ITS RELATION TO CHONDRODYSPLASIA FOETALIS. H. SCHONENBERG and G. SCHALLOCK, Ann. pædiat. **180**:129 (March) 1953.

Description is given of a case of chondrodysplasia calcificans congenita which demonstrates the special position of this illness within the framework of chondrodysplasia fetalis. Other malformations, such as congenital cataract, limitation of extension of the extremities, and hyperkeratoses, were observed. The seven so far reported cases of "stippled epiphyses" are considered to be calcifications of the cartilages without disturbance of the zone of cartilagenous growth. The idea is put forward that the congenital calcifying chondrodysplasia stands between the fetal chondrodysplasia and the constitutional form of enchondral ossification disturbances (type Ribbing). It is assumed that several factors are involved in the pathogenesis of this illness.

FROM THE AUTHORS' SUMMARY.

OSTEOPOROSIS AS EARLY SYMPTOM OF OSTEOCHONDROSIS DEFORMANS COXAE JUVENILIS PERTHES. F. WIRZ, Schweiz. med. Wchnschr. **83**:384 (April 18) 1953.

Listing the x-ray findings in 12 cases of Perthes's disease, attention is called to the osteoporosis as early sign of the disease, which was observed in 9 of these cases. It may be ribbon-like, limited to the vicinity of the epiphysis, or difuse in the rest of the neck of the femur and the upper part of the diaphysis. It may also be seen in the region of the acetabulum and the adjacent region of the pelvis. The osteoporosis is not due to inactivity. Another early sign is a hypoplasia of the lower pelvis on the affected site and a swelling of the soft tissues of the hip joint.

AMBERG, Rochester, Minn.

RADIOGRAPHIC STUDY OF BONE GROWTH. M. SUAREZ, J. PENA, and S. SANZ, Rev. españ. pediat. **9**:101-115 (Jan.-Feb.) 1953.

The bone age, especially in the bones of the hand, is useful in studying development in children and in use in correlation with chronological age. It is an index of sexual maturity also and can be used to predict the adult height of the child.

Nutrition status, history of former illness, evidences of endocrine pathology, etc. are also reflected in the skeletal development of the child.

An outline of the various methods used and the history of the study of bones as an index to growth is included.

ALLEN, Santa Fe, N. Mex.

BIOCHEMICAL STUDY (ALKALINE PHOSPHATASE AND BONE GROWTH). M. SUAREZ and S. SANZ, Rev. españ. pediat. **9**:117-121 (Jan.-Feb.) 1953.

The authors studied the bone age and serum alkaline phosphatase in 165 children from birth to 5 years of age. Also, the determinations of calcium and phosphorus were made. The children were classified according to bone as normal, accelerated, and retarded.

The variations in the velocity of growth expressed in increments in height are parallel to the variations of the alkaline phosphatase in the serum. This was true in all cases, whether bone age was normal, slow, or accelerated.

These findings are the same as those arrived at by Clark and Beck. Graphs and tables, along with details of the technical study, are included.

ALLEN, Santa Fe, N. Mex.

AMYOTONIA CONGENITA. GUSTAVO ROSS, Rev. chilena pediat. **24**:113 (April) 1953.

The author reports four cases of primary spinal muscular atrophy, Oppenheim's disease, or amyotonia congenita.

In the first case, the onset was at the age of 6 months and there was no family history of this disease.

The second case had begun right after birth, and an older sibling died at the age of 5 months from a similar condition.

The third case, like the first one, had no family history, and his symptoms were first noted at the age of 4 months.

In the fourth case, the symptomatology began at 4 months of age, and he had a brother whose illness had begun at birth and who died at the age of 1 year.

The author does not think it is worthwhile differentiating this syndrome from the Werdnig-Hoffmann's, based only on the initiation, progression, or family history, since any of these elements may be found in either of them.

FROM THE AUTHOR'S SUMMARY.

FAMILIAL EARLY INFANTILE MYASTHENIA GRAVIS. B. BORNSTEIN, Acta pædiat. **42**:442 (Sept.) 1953.

A report is given of two cases—two children of a healthy mother—who acquired myasthenia. The diseases appeared in both cases in the third month of life. At the ages of 5 and 7 years, respectively, typical symptoms were present, affecting the eyelid, the face, and the chewing muscles. Neostigmine (Prostigmin) improved the symptoms.

FROM THE AUTHOR'S SUMMARY.

Diseases of Eye

THE CROSS-EYED CHILD: ETIOLOGIC FACTORS IN HIS DEFECT. GEORGE M. HAIK and GEORGE ELLIS, J. Louisiana M. Soc. **105**:191-194 (May) 1953.

The author emphasizes the fact that for proper comprehension of the various etiologic factors responsible for crossed eyes, development of binocular vision is important. While muscular dysfunction is the commonest cause, it must be remembered that other causes may be responsible and that failure to recognize these may have drastic consequences.

McGUIGAN, Evanston, Ill.

MORE OPHTHALMIC DISEASES OF CHILDREN. JOHN SLADE, Clin. Rep. Adelaide Child. Hosp. **2**:123-129 (May-Nov.) 1953.

Common eye diseases of children are briefly outlined, with treatment given clearly and succinctly. Squint is given especial attention, with a plea for early referral to an ophthalmologist.

McGUIGAN, Evanston, Ill.

TIME FACTOR IN THE TREATMENT OF STRABISMUS IN CHILDREN. ALFREDO ARRUGA FORGAS, Acta pediat españ. **11**:1-22 (Jan.) 1953.

The author outlines the types of strabismus, lists the concomitant eye defects frequently present, and gives account of the various modes of treatment for different types of defects.

He deplores the tendency to allow strabismus to go untreated with the expectation that it will improve. This results in loss of vision in one eye, at least.

The ordinary cover test will prove a diagnostic value in a large percentage of cases and can be done by a pediatrician or general practitioner in the course of physical examination. Deviation of less than 15 points requires a minute examination, as strabismus may be incorrectly diagnosed. Sometimes apparent strabismus may be due to other anomalies, such as facial asymmetry, large interpupillary distance, or exophthalmos. The aim in all treatment is the development of binocular vision. Reasons for failure of this are cited. Error in refraction should be corrected after the binocular vision is attained.

ALLEN, Santa Fe, N. Mex.

TUMOR OF THE OPTIC NERVE IN VON RECKLINGHAUSEN'S DISEASE. W. A. MANSCHOT, Maandschr. kindergeneesk. **21**:328 (Oct.) 1953.

The ophthalmological symptoms of von Recklinghausen's disease are discussed. A clinical report is given of two children, a boy aged 13 years and his sister aged 8 years, with a glioma of the chiasma and the optic nerve. Both the children, their mother, and the third child of the family, a twin sister of the boy, showed *café au lait* pigmented patches in the skin. The twins were mentally defective; and intra-abdominal tumor of the size of a cocoanut was found above the symphysis of the boy. Tumors of the optic nerve are seldom encountered. Tumors of the optic nerve associated with von Recklinghausen's disease, however, are relatively frequent. Most of these tumors are gliomas; some of them are endotheliomas. The association between tumors of the optic nerve and von Recklinghausen's disease can no longer be considered a mere coincidence. Attempts to find some common background for all the tumors which make up the von Recklinghausen syndrome are complicated by the fact that pathologists disagree about the nature of these tumors. The clinical features, the therapy, and the prognosis of the tumors of the optic nerve in von Recklinghausen's disease are discussed.

FROM THE AUTHOR'S SUMMARY.

Cutaneous Diseases; Allergy

ERYTHROMYCIN IN TREATMENT OF PYODERMA IN CHILDREN. L. C. FREEMAN and R. B. SCOTT, J. Pediat. **42**:669 (June) 1953.

Freeman and Scott report ten cases of impetigo and secondary pyoderma treated with erythromycin ointment. Treatment was effective, and there was no evidence of drug sensitization.

MACDONALD, Pittsburgh.

ORAL CORTISONE TREATMENT OF INFANTILE ECZEMA. LEWIS WEBB HILL, New England J. Med. **248**:1051 (June 18) 1953.

The author treated 18 eczematous infants under 3 years of age with oral cortisone. The duration of treatment varied from 1½ months to 11 months, and potassium chloride was given to each child. Antibiotics were not used routinely but were employed at the slightest hint of infection. The total maximum daily dose was 75 mg. of cortisone, and other antieczema preparations were used in addition.

Four cases did not respond, eight cases were benefited in a superior fashion, and six cases did only fairly well. The case histories are given in detail.

The author concludes from this small series that the minimum daily dose of cortisone that is compatible with reasonable results should be used. He did not exceed the 75 mg. figure and used less in some instances.

The precautions used in this treatment and the mental reservations applying to the regimen and its results are listed.

Dr. Hill states that the use of parenteral steroid therapy in infantile eczema has no place in the practical day-to-day management of the disease.

WHEELOCK, Denver.

MEDICAL PROGRESS: ALLERGIC REACTIONS TO BEE AND WASP STINGS. HARRY L. MUELLER and LEWIS WEBB HILL, New England J. Med. **249**:726 (Oct. 29) 1953.

The sting of bees and wasps is universally painful and occasionally followed by anaphylactic shock and perhaps even death. Since this latter occurrence seems to be increasing in frequency (though still quite rare), the authors deem the situation worthy of a critical review.

The chief stinging insects involved are the honey bees, bumble bees, paper wasps, white-faced hornets, and yellow jackets. If possible, exact identification is valuable in view of the necessity for preparation of a specific antigen for desensitization. The responsible antigen is distributed generally throughout the insect's body and is not restricted to the venom.

Those who have been previously stung, and hence sensitized, will often show an immediate or slight delayed reaction (local swelling) and in about a week malaise, urticaria, and other symptoms of serum sickness. Subsequent stings then, in these rare instances, may precipitate a shock reaction with respiratory difficulty, constriction in the chest, cyanosis, edema, urticaria, incontinence, etc., with either slow recovery or death. The above dramatic sequence usually begins in a few minutes after the sting, and the authors point out that nonallergic as well as atopic persons may be so sensitized.

Desensitization procedures are a proved valuable aid in preventing a subsequent fatal sting in hypersensitized persons and should be carried out by use of a mixed extract of all the above-mentioned insect bodies unless the insect is positively identified. Injections are given for three years, since a lesser period may provide incomplete protection. A schedule is given and a list of commercial sources of extract provided.

It must be remembered that most of these persons are extremely sensitive, and great caution is necessary in desensitization procedures.

WHEELOCK, Denver.

STUDIES OF THE NATURAL HISTORY OF HERPES SIMPLEX INFECTIONS. G. JOHNSON BUDDINGH, DAVIS K. SHRUM, JAMES C. LANIER, and D. JOSEPH GUIDRY, Pediatrics **11**:595 (June) 1953.

In a detailed study of 12 persons with primary herpetic stomatitis, the virus was recovered from the mouth and stools during the acute stage, convalescence, and for varying periods of time thereafter. The average time period during which virus could be recovered from these sources was 23 days after the onset of the disease. Virus could not be recovered from the blood or spinal fluid, but patients were not available for study before the third day of the disease.

Neutralizing antibodies to herpes simplex were first demonstrated in the serum from the fourth to seventh day of the disease. The antibodies attained a maximum level during the second or third week. Considerable differences in individual antibody levels were noted. The maximum antibody concentration was not maintained and dropped to relatively low levels over varying periods of time in each patient studied.

Herpes simplex virus was recovered from the mouths of many persons presenting no clinical evidence of herpetic infection. The virus was recovered from 7% of 571 normal persons of various ages. It was recovered from one infant out of 97 under 6 months of age, from 20% of 72 children of 7 months to 2 years, from 9% of 199 children 3 to 14 years of age, and from 2.5% of 185 adults. The incidence of normal carriers was found to be highest (26%) in Negro children in the 7-month to 2-year age group.

Neutralizing antibodies were demonstrated in the serum of 43% of white and 71.4% of Negro children in the 7-month to 2-year age group. The serum of 84.7% of white and 86% of Negro children in the 3- to 14-year age group contained antibodies to herpes. In adults, 90% of white and 96% of Negro persons had antibodies to herpes in the serum. Natural active immunity appears to be established at an earlier age in the segments of the population in which the highest carrier rate was demonstrated.

Neutralizing antibodies were demonstrated in the serum of 76% of white infants and in 90% of Negro infants 6 months of age and under. The placental transmission of neutralizing antibodies was demonstrated. Approximately the same level of antibody was found to be present in the maternal serum and in the serum obtained from the placenta.

FROM THE AUTHORS' SUMMARY.

PINK DISEASE AND TEETHING POWDERS. BEN EPSTEIN, South African M. J. **27**:823-827 (Sept. 19) 1953.

Thirty-one cases of pink disease are reported. Twenty-two of these were examined for excretions of mercury per liter.

Seventeen controls who had been given teething powders were checked. Thirteen had less than 100 γ per liter.

There is increasing evidence of a greater tendency to pink disease in infants who have been given mercury.

McGUIGAN, Evanston, Ill.

COMPLIMENT FIXATION ANTIBODIES AGAINST ARTICLES OF FOOD IN CHILDREN. E. BERGER, Ann. pædiat. **181**:295 (Nov.) 1953.

Using the complement fixation test, it is shown that children can form antibodies against enteral cow's milk, soya bean protein, and oats.

The complement-fixing antibodies could be demonstrated in strong antigen concentration and in weaker antigen dilutions, i. e., in the so-called right and left zones, respectively.

A case of cow's-milk allergy was tested repeatedly with serological methods, with the result that when the complement-fixing antibodies disappeared, toleration of cow's-milk was achieved.

Based on the material in hand, the question was discussed as to what importance should be attached to the finding of complement-fixing antibodies for the diagnosis of allergic diseases as well as for the nutritional physiology and the resorption of proteinous antigens.

Investigations for antibodies were carried out in 84 children with positive results in 20 cases, i. e., about 24%.

FROM THE AUTHOR'S SUMMARY.

A NEW METHOD OF TREATMENT OF LEINER-MOUSSOUS DISEASE. A. MOYS, Pediat. listy **8**:141 (June) 1953.

The author describes the therapeutic effect achieved by a group of workers (Treger, Moys, and Muzikova) in nine cases of Leiner's disease, with intracutaneous administrations of an aqueous solution of potassium sulphate.

FROM THE AUTHOR'S SUMMARY.

OPTIMAL AGES FOR ELECTIVE SURGERY IN INFANTS AND CHILDREN. COLIN C. FERGUSON, Canad. M. A. J. **69**:381-386 (Oct. 6-9) 1953.

Various surgical procedures for corrections of congenital defects are considered and the most satisfactory time for such repair indicated. With the exception of harelip, repaired at 4 to 8 weeks of age, and inguinal hernia, done at any age, most procedures of any magnitude are deferred until 3 years of age or later. Brief notes are included covering operative techniques and procedures of choice.

McGUIGAN, Evanston, Ill.

THE TREATMENT OF BURNS. J. T. GROND, Nederl. tijdschr. geneesk. **97**:1007 (April 18) 1953.

The author gives a survey of the modern treatment of burns. First, the problem of shock is discussed—its cause, physiology, and treatment. As a most important factor, diuresis is mentioned as a guide for the replacement of the fluid loss. If the diuresis is not large enough, the syndrome of lower nephron nephrosis may develop. Second, infection should be attacked effectively. Sulfonamides are contraindicated because of the danger of crystal formation in the renal tracts. Each case should be considered according to its merits. The wound should be dressed under the strictest aseptic conditions. The surface of the wound should be clean before any grafts are applied. This may take as long as a fortnight. Open treatment of the wound is, according to the author, of advantage. Air conditioning is required to prevent secondary infection.

VAN CREVELD, Amsterdam.

Surgery and Orthopedics

DIFFERENCE IN THE CARIES-PRODUCING EFFECTS OF TWO PURIFIED DIETS CONTAINING THE SAME AMOUNT OF SUGAR. WINFREY WYNN, JOHN HALRI, JAMES H. SHAW, and REIDER F. SOGNNAES, J. Nutrition **50**:267 (June 10) 1953.

Litter mates of both albino rats and cotton rats were fed two synthetic diets that differed quantitatively in a considerable number of their constituents but were identical in their sugar content. Wynn and co-workers concluded from these experiments that dietary factors other than sugar account at least in part for the previously noted difference in cariogenicity between the Emory and Harvard diets. They concluded that since their experiments definitely show a difference in cariogenicity related to constituents of the diet other than sugar, it remains to be determined what these constituents are and in what manner they make the teeth more or less resistent to dental caries. Further investigations are in progress in their laboratories.

FREDEEN, Kansas City, Mo.

Teeth and Dentistry

RELATIVE CARIOGENICITY OF SUCROSE WHEN INGESTED IN THE SOLID FORM AND IN SOLUTION BY THE ALBINO RAT. JOHN HALDI, WINFREY WYNN, JAMES H. SHAW, and REIDER F. SOGNNAES, J. Nutrition **49**:295 (Feb. 10) 1953.

Haldi and co-workers present this study to determine whether sucrose in the solid form is more or less cariogenic than sucrose in solution. Albino rats of the Wistar strain developed no carious lesions when they were fed entirely by stomach tube a high sucrose diet which had previously been shown to be cariogenic when ingested orally. In these experiments, no other food but sugar came into contact with the external surfaces of the teeth, and the only variable was the physical state of the sugar fed orally. Conditions conducive to dental decay were most severe because the animals had to be desalivated. In spite of the severity of these conditions, the number of carious lesions and the caries score, from the absolute point of view, were very low when sugar was ingested in solution. These same values, which are indicative of the incidence and extent of caries, were relatively high when sugar was eaten in the solid form. The cariogenicity of sucrose in these experiments was greatly reduced by dissolving the sugar in water before ingestion.

FREDEEN, Kansas City, Mo.

WHY DO SMALL WOUNDS OF THE AFIBRINOGENEMIC PATIENT NOT ALWAYS BLEED FOR LONGER PERIODS? K. LENGGENHAGER, Schweiz. med. Wchnschr. **83**:334 (April 4) 1953.

A now 14-year-old boy whose blood is free of any trace of fibrinogen has been observed at intervals. Small traumas on fingers, hands, and other parts of the body healed without prolonged bleeding. The same was true for the prick of a blood lancet. In case of other traumas, bleeding was much prolonged. Comparing the platelets of this patient with normal platelets by means of the electron microscope, striking differences were found. These platelets have many more pseudopodia. These can mat together and adhere to fresh wounds. It is proposed to call these platelets "Fangarm" (tentacle) thrombocytes or Medusa thrombocytes.

AMBERG, Rochester, Minn.

HORMONAL REGULATION OF DENTITION. L. G. BAUME, Schweiz. med. Wchnschr. **83**:560 (June 13) 1953.

The effect of thyroid and hypophyseal hormones on dentition was studied in the rat. The thyroid hormone stimulates growth and eruption of the teeth. Growth hormone affects the growth of the teeth more than thyroid hormone, but it can not accelerate the eruption after hypophysectomy. For detail the paper is to be consulted.

AMBERG, Rochester, Minn.

Miscellaneous

SOME COMMON PEDIATRIC ACCIDENTS. J. KELLER MACK, Illinois M. J. **103**:288-291 (May) 1953.

Accidents in Illinois in 1946-1949 killed 10 times as many children as did polio, and it crippled more children too. Accidents are the number one killer between the ages of 1 and 2 years. Accident death rates have decreased, but not nearly as much as the rates for many diseases. In 1930, accidents were the third cause of death. In 1950, accidents were the first cause of death.

In stressing the preventive aspects of accidents rather than the treatment, Mack points out that there are a number of fundamental problems that make accident prevention much more difficult than disease prevention. We are sometimes pitted against our fellow man and even against some fundamental characteristics of human nature. In most accidents, we find somewhere along the line the human touch operating as a known or unknown factor. In safety education, it is necessary to correlate both elements in the accident picture—human nature, and the nature of the things and forces with which human beings come in contact.

It is the adventurous characteristic of human nature that adds to the dilemma in safety education. This human characteristic poses a major difficulty, and the only way to counteract it is to use constructively the craving for excitement and the love of adventure. In all accident prevention we need to weigh these fundamental factors of the neutral quality of the inanimate factor of most accidents, our need to evaluate the human role in learning to use safely these inanimate objects, our fundamental drive for change, excitement, and taking a chance, and the element of boredom in waging a "cold" war against accidents.

The general practitioner and the pediatrician are best able to educate the parents of the toddler, who is the most accident-prone person. We can talk to parents and bring the problems to their attention. In addition, we can prepare mothers for certain developmental periods which can be dangerous. If we are accident conscious, we can impress the parents, who in turn can help to educate the child.

There are 12,000 children killed annually in auto accidents, and for every one of these, 6 go to the hospital and 2½ are permanently injured. Burns cause 28% of accident fatalities in the group 1 to 4 years of age. This group ranks second only to transportation fatalities. Some burns result from the actions of other people, such as spilt liquids or burning houses, but probably most are caused by the person's own mistake. Statistically, drownings come next in the accident causes of death. Minor falls and injuries are of educational value, and a certain amount of pain is a good teacher. In the problem of accident-proneness, there are two factors, physical and emotional.

The parent must steer a middle course between overprotection and indifference, just as the doctor must steer a course between frightening parents about acccidents and indifference to the problem. For prevention of poisonings, the physician can do something specific in the way of warnings and instructions to parents regarding drugs and household chemicals.

This multiplicity of causes is one of the difficulties in accident prevention, because neither patient, parent, nor doctor can always remember all the hazards. In addition to doing what we can in our personal relationships with our patients, we should also play an active part in safety programs in our communities in cooperation with the many agencies interested in child safety.

BARBOUR, Peoria, Ill.

ACCIDENTAL POISONING IN CHILDHOOD. J. O. CRAIG and M. S. FRASER, Arch. Dis. Childhood **28**:259-267 (Aug.) 1953.

Evidence is presented to show that accidental poisoning has been increasing in the child population since 1948. The sources of poison are (1) household substances: disinfectants, fuels, cleaning agents, and insecticides; (2) medicines for internal and external use: nose drops, eye drops, and liniments; (3) vegetable matter.

Poisoning is one of the minor accidents of childhood. For every child who dies of poisoning, 20 are killed on the road. Poisoning is on the increase, but most of this increase is due to medicinal poisons.

KELLY, Milwaukee.

FAVISM IN LONDON. JOHN H. BIGGLE, Arch. Dis. Childhood **28**:369-371 (Oct.) 1953.

Two cases of favism in Cypriot boys are described. The younger child had a severe attack with hemaglobinuria and required a large blood transfusion. The older child had a milder attack without hemaglobinuria but with jaundice.

The diagnosis is discussed and attention is drawn to the importance of eliciting a history of the ingestion of broad beans within two days before the onset of the illness.

KELLY, Milwaukee.

POISONING BY THE VOLATILE OILS IN CHILDHOOD. J. O. CRAIG, Arch. Dis. Childhood **28**:475-483 (Dec.) 1953.

It is pointed out that the volatile oils as a group head the morbidity and mortality lists for accidental poisoning in childhood. Camphorated oil and oil of turpentine are the oils most commonly ingested, but methyl salicylate (oil of wintergreen) accounts for three times as many deaths as camphor, the second commonest lethal agent. The symptoms and treatment of poisoning by camphor, eucalyptus, sassafras, turpentine, and methyl salicylate are discussed. It is suggested that the sale of these dangerous poisons, with the exception of turpentine, be controlled.

KELLY, Milwaukee.

BORIC ACID POISONING IN INFANCY ARISING FROM THE TREATMENT OF NAPKIN RASH. P. C. MACGILLIVRAY and M. S. FRASER, Arch. Dis. Childhood **28**:484-488 (Dec.) 1953.

A nonfatal case of poisoning of a young infant resulting from the treatment of napkin rash with powdered boric acid is reported.

The main clinical features were vomiting and diarrhea, with slight gastrointestinal bleeding, convulsions, and a rash on the face and extremities. The type of poisoning may readily be confused with infective gastroenteritis.

Both boric acid and mercuric chloride are undesirable susbtances for the treatment of napkin rash. Safe and effective alternatives are available.

Boric acid is a potentially dangerous drug and is only feebly antiseptic.

KELLY, Milwaukee.

HAEMANGIO-ENDOTHELIOMA WITH HAEMORRHAGE AND THROMBOCTOENIA. A. WHITE FRANKLIN and D. A. J. WILLIAMSON, Arch. Dis. Childhood **28**:490-494 (Dec.) 1953.

Two cases are described in which hemangioendotheliomata in the neck were associated with thrombocytopenic purpura. In both cases, hemorrhages occurred into the tumors, producing serious respiratory embarrassment. Three similar cases from the American literature are briefly reviewed. Features common to the group are rapid enlargement, invasion of the deeper structures and x-ray changes in underlying bone, recurrent hemorrhage and accompanying thrombocytopenic purpura, anemia and prolonged bleeding and clotting times, sensitivity of the tumor to x-rays, and perhaps a predilection for the tissues of the neck.

KELLY, Milwaukee.

SUMMARY OF ONE HUNDRED SIX POST-MORTEM EXAMINATIONS PERFORMED DURING 1952. RUTH OSMOND, Clin. Rep. Adelaide Child. Hosp. **2**:158-163 (May-Nov.) 1953.

The two largest causes of death in the series were congenital anomalies (17%) and bronchopneumonia and gastroenteritis, which together caused 21%. Atelectasis was found in 7.5%. There were three cases each of laryngotracheobronchitis and rheumatic fever. Five per cent of cases were fibrocystic disease. Only two cases of brain abscess were included; 6% of deaths were due to meningitis, and 3% to mastoiditis.

McGUIGAN, Evanston, Ill.

MERCURY INTOXICATION IN CHILDHOOD. J. G. WILSON, Clin. Rep. Adelaide Child. Hosp. **2**:164-167 (May-Nov.) 1953.

Four cases of mercury intoxication were admitted during 1952. Two had been given mercury-containing teething powders, one had been treated for eight months with a mercury-containing ointment, and the other gave no history of possible mercury intake. The similarity of chronic mercury poisoning to acrodynia is again pointed out.

McGUIGAN, Evanston, Ill.

THE ADOPTION AND FOSTERING OF CHILDREN. MARJORIE GILCHRIST, M. J. Australia **1**:445 (March 28) 1953.

Complete psychiatric investigation should be made of both the child and the prospective parents. Adoptive or foster parents who take a child who has been deprived of parents for a

long time must be especially stable. Unless the child is only 2 to 3 weeks old, mental health is of paramount importance. Presence of psychological disturbances of any type should be a bar to adoption by such parents.

McGUIGAN, Evanston, Ill.

THE PULMONARY ADMINISTRATION OF CALCIUM GLUCONATE TO CHILDREN. M. GOMIRATO SANDRUCCI and P. GAMALERO, Minerva pediat. **5**:177 (March 31) 1953.

Seventeen observations on children 4 to 11 years old revealed that the giving of calcium gluconate solution as an aerosol resulted in an appreciable rise in the blood calcium percentage. Two methods of giving the calcium gluconate were employed; in one the child was kept in a room with a capacity of 40 cubic meters for three days, a solution of 2% calcium gluconate dissolved in boric acid being sprayed into the room. In the other method, a mask was used with an aerosol containing 0.10 gm. per kilogram body weight. In the chamber test, the blood calcium had risen 22% after eight hours and then fallen to a rise of 8% after 72 hours. In the mask group, the blood calcium had increased a maximum of 12% one hour after the inhalation had been discontinued; one and one-half hours later, it was still 3.5% above the amount found before the test began.

HIGGINS, Boston.

THE DIFFUSION OF VIOMYCIN IN THE PARENCHYMATOUS ORGANS. G. BELLIENI and R. BIAGINI, Riv. clin. pediat. **51**:464 (Dec.) 1953.

The authors have studied the diffusion of viomycin in parenchymatous organs. They noted that viomycin on reaching high levels in blood-serum passes into the kidneys as well as liver and lungs. When the doses of the antibiotic decrease, viomycin disappears first of all from the liver and lungs and then from the kidneys. The fact that viomycin is eliminated through urinary organs may account for this. The authors note that a high concentration of viomycin is required in the blood in order that the organs may contain it.

FROM THE AUTHORS' SUMMARY.

HYPERSENSITIVITY TO SULFONAMIDE PREPARATIONS (TREATMENT WITH CORTICOTROPIN [ACTH]). C. G. SYPKENS SMIT, L. MEYLER, and S. DUURSMA, Nederl. tijdschr. geneesk. **97**:85 (Jan. 10) 1953.

Case histories are given of two patients who were severely ill with fever and a rash, headaches, apathy, paralysis of limbs with low reflexes and neuralgias, vomiting, diarrhea, jaundice, and enlargement of liver and spleen. In one patient, hyperesthesia together with anesthesia was found. No changes in the cerebrospinal fluid could be demonstrated. Both patients recovered gradually in a few weeks, when no more sulfonamide medication had been given. Corticotropin (ACTH) was thought to be of great benefit in one patient in whom it was used. A third patient, who was suffering from carcinoma of the skin and pneumonia, was treated with 5 gm. of sulfadiazine per day. Severe necrotising arteritis was found in lungs, spleen, and liver at the postmortem examination.

VAN CREVELD, Amsterdam.

EXTRAPULMONARY GAS EXCHANGE. H. VAN GOOR, Nederl. tijdschr. geneesk. **97**:147 (Jan. 17) 1953.

Injection of 300 ml. of oxygen in the stomach of anesthesised rabbits decreases the oxygen uptake in the lungs about 30%. After injection of 300 ml. of carbon dioxide, the alveolar carbon dioxide output remains practically unchanged. The supposition is that carbon dioxide which leaves the stomach will be hydrated to carbonic acid in presence of carbonic anhydrase, thus providing hydrogen ions for hydrochloric acid production. After rectal administration of 300 ml. of oxygen, about 25% of the total oxygen requirement is secured by extrapulmonary diffusion. Oxygen perfusion of the intestines decreases the alveolar gas exchange about 50%. If during oxygen perfusion the trachea is clamped, the time of survival of the experimental animals varies from 12 to 16 minutes.

VAN CREVELD, Amsterdam.

HEARING IMPAIRMENT AND ITS DEVELOPMENT CAUSED BY STREPTOMYCIN. T. TAKAFUJI and G. FURUYA, J. Oto-Rhino-Laryng. Soc. Japan **56**:712, 1953.

Takafuji and Furuya observed hearing impairment as a toxic effect of streptomycin therapy in 50 patients with tuberculosis.

There were two groups: Group I (30 cases) included those patients with pulmonary tuberculosis who had been treated by intramuscular injection of streptomycin, while Group II (20 cases) included patients with tuberculous meningitis who had been treated by the combination of intrathecal and intramuscular injections of streptomycin.

Most (38%) of those in Group I showed high-tone deafness in the audiogram, and their degree of hearing impairment was moderate or slight.

More than half (59%) of those of Group II showed total deafness.

The audiograms of Group I showed an abrupt dip at 4,000 db. in the beginning, and later there was a gradual slope in the high-tone ranges. Finally, the audiogram assumed a flat form involving low and high tones.

In Group II hearing was affected greatly for one to two months, and finally severe or total deafness developed.

From these observations Takafuji and Furuya state that the primary lesion obviously begins at the end-apparatus of the cochlear nerve as a degenerative process, and it probably proceeds to the acusticus nerve in the form of "retrograde ascending degeneration."

HARA, Los Angeles [A. M. A. ARCH. OTOLARYNG.].

News and Comment

ANNOUNCEMENTS

Pediatric Reunion in Honor of Dr. McQuarrie.—In honor of 25 years of distinguished service to the University of Minnesota, Dr. Irvine McQuarrie, head of the department of pediatrics, will be honored at a pediatrics grand reunion, Sept. 23-25, at the University.

Colleagues and students of Dr. McQuarrie have planned the reunion in conjunction with the annual Northwestern Pediatric Society meeting.

Lectures will be delivered at the meeting by 22 academic leaders in the field of pediatrics. Most of them received their pediatric training under Dr. McQuarrie.

As an additional tribute to the University pediatric chief, a McQuarrie Pediatrics Fund has been established, with a goal of $50,000. An annual source of income from it will be earmarked to provide a lectureship in pediatrics, as a scientific travel fund for pediatrics staff members to attend special conferences, to provide fellowships in unusual circumstances, to provide necessary equipment that may be needed from time to time by the department, and for any other purpose within the department as approved by the committee.

Dr. McQuarrie, a graduate of the University of Utah, who received his doctor of philosophy degree from the University of California and his doctor of medicine degree from The Johns Hopkins University, joined the University of Minnesota staff in 1929.

Before coming to Minnesota he had served on staffs of the University of California, Henry Ford hospital, Yale university, and the University of Rochester. And in addition to his duties at the University during the past 25 years, he was visiting professor of pediatrics at Peking Union Medical college, in China, and served on the China Medical Board of Rockefeller Foundation.

Lecturing assignments on pediatrics have taken him to the far corners of the world, including Japan, Brazil, Uruguay, Argentina, Chile, Peru, Canada, Mexico, Italy, Cuba, and China.

Dr. McQuarrie is editor-in-chief of "Brennemann's Practice in Pediatrics" and is an associate editor of 10 medical publications.

In addition to his personal contributions to the field of pediatrics, men trained by him are now spreading his educational theories on pediatrics in such places as the Universities of Texas, Louisiana, California, Iowa, Utah, Colorado, and Oregon, as well as Tulane University, Meharry College, Stanford University, and Peking Union Medical college.

Two Courses in Pediatric Hematology for Practitioners.—The course in Practical Pediatric Hematology received with such success in the past two years will be repeated on Sept. 13, 14, and 15, 1954. It will be under the direction of Dr. Irving J. Wolman, Associate Professor of Pediatrics and Director of Laboratories of The Children's Hospital. Dr. Wolman will be assisted by Dr. Benjamin Dickstein, Dr. Paul G. Eglick, Dr. Timothy Talbot, Dr. George Ward, and others.

The following subjects covered will be: hemoglobin, erythrocytes, leucocytes, and platelets, with normal values as related to age, prematurity, etc.; demonstrations and interpretation of the bone marrow examination; approaches to the investigation of the anemias, Mediterranean anemia, sickle cell anemia, hereditary sperocytosis, acquired hemolytic anemia, the malnutritional anemias, anemias secondary to toxic and systemic disturbances; splenomegaly and related disturbances; the hemorrhagic diseases, such as the purpuras, the hypoprothrombinemias, and the newly recognized subvarieties of hemophilia; infectious mononucleosis and other disorders of the leucocytes; diagnosis and management of leukemia; advances in transfusion therapy.

These topics will be presented from the standpoints of normal and abnormal physiology, clinical and laboratory recognition, and the latest concepts of therapy. There will be case presentations, conferences, and demonstrations of new diagnostic approaches within the scope of the average office laboratory.

Each physician in attendance will receive a collection of representative blood and bone marrow smears.

The tuition fee is $60.00.

A new course on Rh and Other Blood Group Incompatibilities in Relation Erythroblastosis Fetalis will be given on Sept. 16 and 17, 1954 under the direction of Dr. Neva M. Abelson, Assistant Professor of Pediatrics and Director of the Philadelphia Serum Exchange Division of The Children's Hospital.

The topics to be covered in the two-day course are as follows:

Thursday, Sept. 16 . . . Erythroblastosis fetalis: clinical management (including exchange transfusion)

Friday, Sept. 17 . . . Laboratory procedures: Rh and other blood group incompatibilities

The tuition fee is $40.00.

These courses will be given at the Children's Hospital of Philadelphia and will run from 9:30 a. m. to 4:30 p. m. daily.

For application forms address:

The Dean
Graduate School of Medicine
230 Medical Laboratories
University of Pennsylvania
Philadelphia 4, Pennsylvania.

GENERAL NEWS

Joint Meeting of Institute of Medicine of Chicago and Chicago Pediatric Society.—The first joint meeting of the Institute of Medicine of Chicago and the Chicago Pediatric Society was held at the Drake Hotel on March 16, 1954. The scientific program included "Paul Ehrlich's Contribution to Pediatrics," by Dr. Hans C. S. Aron, which was published in full in the *Journal of the American Medical Association* on March 20, 1954, and "Metabolic Functions of Vitamin C," by Dr. Charles D. May, which will be published in full in the *Proceedings of the Institute of Medicine of Chicago.*

PERSONAL

Appointment for Dr. Alex J. Steigman.—Dr. Alex J. Steigman, Professor of Child Health, has been appointed Chairman of the Department of Pediatrics at the University of Louisville School of Medicine, where he has taught for the past four years.

Books

Synopsis of Pediatrics. By John Zahorsky. Price, $7.50. Pp. 470, with 158 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1953.

This book is an organized synopsis of pediatrics. It is well written and makes for easy reading. The authors mention in their preface that this book is strictly a condensation, and that a regular textbook or up-to-date literature must be consulted for details.

The sections on contagious disease and vitamin deficiencies are especially well written.

While the description of the various conditions in regard to cause, symptomatology, and physical findings is satisfactory, the discussion on treatment is most inadequate. The authors did very little revision of the previous editions on this particular and important phase of pediatrics. Most therapeutic measures mentioned are ancient, with very little emphasis on modern therapy. A few examples of this are as follows: In discussing treatment of acute cervical adenitis—hot and cold compresses, stimulating ointments, such as 5% ichthammol (Icthyol), iodine ointment, turpentine liniment are discussed in a full paragraph, with the concluding sentence that "sulfonamides or antibiotics should be prescribed." The use of intramuscularly administered whole-blood transfusions, without benefit of typing or cross-matching, with the parents as donors, is advocated for the treatment of hemorrhagic disease of the newborn. Camphorated oil or spirits of chloroform for local treatment of bronchitis is also noted in this text. Frequent tapping of a hydrocele is discussed in the same breath as surgical correction. Intussusception is treated by the authors as follows: "The infant is anesthetized, tumor grasped through the abdomen and tightly squeezed to reduce its congestion. Then the body is shaken up and down and from side to side. This is repeated several times." When this fails, surgery is undertaken.

The appendix of the book, which deals with management of medical emergencies, is supposed to be especially valuable to the student, intern, or general practitioner. However, here again there is no specificity or details of treatment, and what is mentioned is most antiquated. The discussion of intestinal intoxication with dehydration which is a most important pediatric problem is poor. There is no reference made to calculating fluid loss or any means of replacing it by the use of specific electrolytes.

This textbook could be an excellent synopsis of pediatrics if an effort were made to revise the sections on therapy. The authors could do this by being more specific regarding the use of modern drugs and by eliminating the descriptions of the antiquated symptomatic treatment which is so prevalent in this monograph.

Holt Pediatrics. Edition 12. By L. Emmett Holt Jr. and Rustin McIntosh. Price, $15. Pp. 1542, with 269 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York, 1953.

The previous edition of this traditional mainstay of the pediatric library is so long obsolete that the present edition is actually a completely new text. In accordance with the present trend, Holt is now a composite book written by 72 authors. The list of collaborators is indeed an impressive one.

Previous editions of Holt were noted for their conciseness and readability as compared to other texts. The present volume continues this tendency to be brief and concise, though in a few places the conciseness is overdone to a point of insufficiency.

Although this is a completely new book, it would be useless to try to review all of the sections in detail. Almost all the articles are good, adequate in coverage, and reflecting the most current thinking. Worthy of mention as exceptionally good are the sections on neurology and endocrinology. Diabetes is well covered. The section on the newborn is perhaps less satisfying than one would like, though well written.

A few points that are irritating, at least to this reviewer, may be mentioned; owing to the material having been written by different authors under varying headings, there is no compre-

hensive section on meningitis. Instead it is necessary to refer to the index in order to find each particular type. Also, this field in general is too briefly covered. It is gratifying to note the avoidance of intrathecal therapy.

In general discussion of corticotropin (ACTH) and cortisone, only three pages are used. This seems to be brief. The section on poisoning is brief, weak, and noninclusive. A brief table in the appendix is the only source of information for most poisons, and even here medicinal agents are omitted, the physician being left to his own recollection of the pharmacology and toxicology involved.

The physical appearance of the book is pleasing, the typography and binding being excellent. Reproduction of illustrations is good. The pages are not divided into two columns, a recent trend which has not seemed advantageous to this reader. As regards the index, it is not as complete as some, and seems rather brief. It is 30 pages long, with two columns to the page. Even the old 10th edition had 47 pages, and a current text, too, 37 pages of three columns each.

All in all, Holt is a good text, better perhaps for the student than the well-grounded practitioner. It is well up to the reputation it had previously established. Perhaps its reception will encourage the editors to prepare more frequent editions in the future.

Developmental Psychology. By Elizabeth B. Hurlock. Price, $6. Pp. 556, with 60 illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1953.

This is a book of 556 pages of the knowledge that has been put into the written word by the students of the thought and behavior of mankind. Elizabeth Hurlock has written of her bibliography of over a thousand writings in a manner that indicates orderly intake, digestion, and assimilation of the literature that deals with the evolution of the human personality. The effects on the mind of the constancy of change of the body are kept before the reader, changes inherent in growth and aging, also the difference between man and woman. The division of human life into 10 periods is used to enumerate and describe the qualities more clearly shown in each period. In citing these qualities the reasons for their appearance are discussed, also the influence the quality may have in the general process of development of the personality. There is one chapter of 33 pages, "The Mature Adult," in which the maladjusted and the well adjusted are documented and compared. Throughout the book the differences in thought and action of the two sexes is constantly kept before the reader. If there is a science of human thought and behavior, Dr. Hurlock has done a masterful job in collecting and documenting what has been written in pursuit of progress in that field of knowledge. However, the constancy of change, the inevitable companion of growth, learning, and the passage of time, makes the fitting of human mind and behavior into the rigid patterns of science largely a matter of the ability to use words. Dr. Hurlock and her conclusions seem ready to respond to changes that science may evolve. She avoids offending the worshipful rigid patterns of right and wrong, of good and bad. In Chapter I "Growth and Decline," human life is divided into 13 periods: 2 prenatal, 3 infancy, 2 childhood, 2 adolescent, 2 maturity, and 2 senescence. Each is marked by physical and social characteristics. In Dr. Hurlock's writing of development the life span is divided into 10 periods, each with its outstanding characteristic. One might say that the importance of imitation is slighted, especially if one bears in mind the role that speech plays in human life and that speech must be like that of those we learn from and grow up under. If a man had written this book he might have made competition more of a factor. This is an American book written in the atmosphere of the English language. It had to be written and published, and it has to be read.

The Pharynx: Basic Aspects and Clinical Problems. By Abraham R. Hollender. Price, $15. Pp. 560, with 31 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1953.

In this monograph the author and his collaborators offer a comprehensive survey of their subject. In the opening section, titled "basic aspects," anatomy, physiology, pathology, bacteriology, roentgenology, and methods of diagnosis are thoroughly covered. The clinical problems are dealt with in 24 succeeding chapters.

The book is essentially a summary of current opinion regarding the pharynx and its disorders, with thorough documentation and sizeable reference tables at the end of most chapters. The author has chosen to introduce and conclude the various chapters with editorial comment.

Commendable emphasis is placed upon the pharynx in relation to the body as a whole, and the pharyngeal manifestations of blood diseases are especially well presented. A chapter on the psychosomatic aspects or oral and pharyngeal disease points to increasing recognition of the importance of this field in modern medical practice. Also deserving of comment are the excellent chapters on neoplasms of the mouth, oropharynx, and nasopharynx.

The best illustrations in this book are those which have been reproduced from other texts or articles. The photographs in general are satisfactory, but the original drawings and roentgenograms are poor. A few unorthodox concepts will doubtless arouse disfavor in the critical reader.

The purpose of the author will have been served if one accepts the premise that there is need or justification for a book devoted exclusively to the pharynx. This treatise probably warrants perusal by otolaryngologists and pediatricians and might well serve as a valuable reference source.

Familial Nonreaginic Food-Allergy. Edition 3. By Arthur F. Coca, M.D. Price, $10.50. Pp. 281, with 48 tables, 21 charts, and 26 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

Dr. Coca's monograph "Familial Nonreaginic Food-Allergy" is now in its third edition, which attests to the fact that many are interested in this adventure into the field of allergy.

Dr. Coca has enlarged his book to include chapters on the diagnostic and prognostic use of the stellate ganglion block, the relation of this form of allergy to poliomyelitis paralysis, its relation to hypertension, multiple sclerosis, tobacco sensitivity, glaucoma, and other disease states.

The main thesis of this volume is that certain persons, who are sensitive to food but do not present positive skin reactions, regularly have an acceleration of the pulse rate during an allergic episode. Upon this thesis is based "a new method of approach" to the diagnosis and treatment of a group of allergic diseases.

Dr. Coca has termed this form of allergy "idioblapsis" and does not believe it depends on an antigen-antibody mechanism. "Idioblapsis" may satisfy a need for those who will not wholly accept the antigen-antibody mechanism as the basis of the allergic reaction.

Though there may be a shadow of real merit to Dr. Coca's hypothesis, it appears to this reviewer that too much ground is covered with not enough sound scientific support.

Allergy has traveled on many tortuous paths, and this seems a strange one indeed. Perhaps the pulse rate does increase during allergic episodes, as it does in many physiological disturbances. Surely this symptom is an extremely fickle one, and it seems difficult to conceive that it can be regarded of special significance in the evaluation of so chronic and insidious a condition as allergy. Furthermore, the short range of pulse rate increase that Dr. Coca regards as pathognomonic would not be impressive to those interested in children, who think nothing of a bounding pulse of 120 or over resulting from countless causes.

The subject of allergy is still suffering from too many unsound theories, unsound practices, and unsound therapeutic agents. The basic antigen-antibody principles are sound and should be fortified by continued studies and developed to their fullest potentialities.

Human Embryology. Edition 2. By Bradley M. Patten. Price, $12. Pp. 798, with 453 illustrations and 2 plates. Blakiston Company, 575 Madison Ave., New York 22, 1953.

This new edition of a widely used textbook in embryology contains two important improvements. Chapters 4, 5, and 6 have been modified by the introduction of new figures and text material dealing with recent advances in our knowledge of early human development. Chapter 19 has been enlarged to permit the inclusion of additional information about the anomalous development of the cardiovascular system, especially that of the heart and great vessels. The other chapters remain as they appeared in the first (1946) edition except for minor improvements. A supplementary bibliography covering the last seven years is a valuable addition.

This text is an excellent one for advanced undergraduate and graduate courses in human embryology. The first-year medical student will use it constantly in his anatomy courses and will refer to it frequently during his clinical years.

Störungen der Fettresorption im frühen Säuglingsalter. By Fritz Hauser. Price, 14 Swiss francs. Pp. 108. S. Karger, Holbeinstrasse 22, Basel; Agent for U. S. A. Interscience Publishers, Inc., 250 5th Ave., New York 1, 1953.

Conditions with poor resorption of fat from the intestine are frequent in infancy. They include prematurity, acute diarrheal disorders, cystic fibrosis of the pancreas, celiac disease, obstruction of the bile ducts, and icterus gravis.

Hauser's monograph, based on a large amount of clinical and laboratory studies, represents a valuable contribution to the subject. The laboratory methods used by the author include analysis of fat in the stool, determination of pancreas enzymes in the duodenal juice and of trypsin in the stool (gelatine film test), the vitamin A absorption test, and the count of chylomicrons in the blood.

Obstruction of bile flow produces severe impairment of fat resorption. The obstruction may be due to congenital malformation of the bile ducts, to inflammatory diseases of the liver, or to icterus gravis with excessive hemolysis. Differential diagnosis is important, since congenital malformation of the bile ducts requires surgery.

Among the disturbances of fat resorption due to diminished or absent pancreas enzymes, pancreatic fibrosis is of major importance. The fat losses in this condition may be as high as 80%. The duodenal juice showed in all cases a high degree of viscosity. Diagnostically, the vitamin A test and the gelatine film test proved to be of great value. Concerning the different clinical types of pancreatic fibrosis, the author follows B. Andersen's classification in (1) cases with meconium ileus, (2) cases with early onset of respiratory infection, and (3) cases with late onset of respiratory infection.

The treatment of pancreatic fibrosis consisted of pancreas preparations, diet, vitamins, penicillin, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin). Lung complications responded promptly to the latter two drugs, and the foul odor of the stool disappeared instantly.

A final chapter of the monograph deals with the influence of age and maturation on the resorption of fat. Impaired fat resorption occurs in young full-term as well as in premature infants. In full-term infants the fat resorption becomes normal within two to three weeks. Premature infants show more severe and longer-lasting fat losses in the stool. The utilization of fat is better in infants fed raw breast milk than in infants fed sterilized breast milk, apparently due to the fact that the sterilization destroys the milk lipase.

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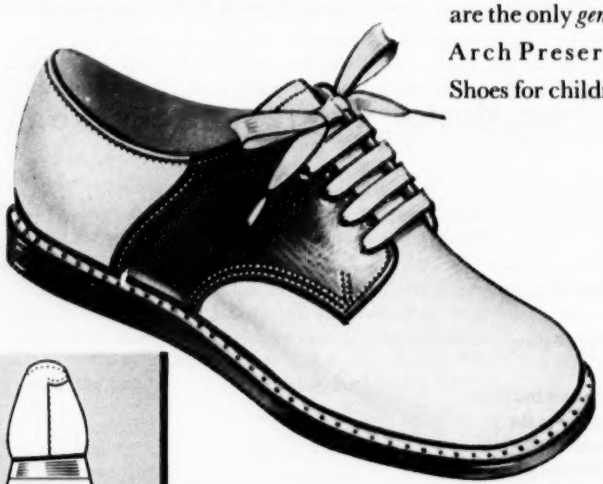

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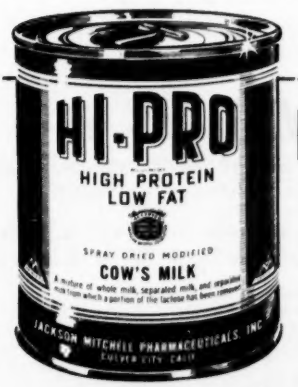
[1]Jeans, P. C. & Marriott W. McK. Infant Nutrition; 4th ed.
[2]Holt, E. M. Diseases of Infancy; 11. 223.



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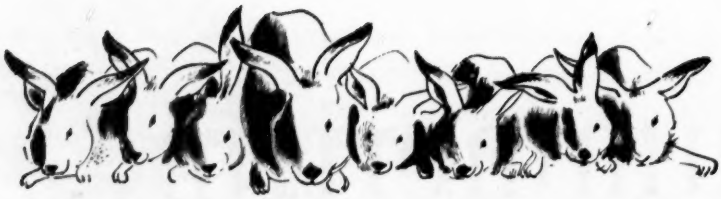

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1. Herrington, B. L.: Milk and Milk Processing. New York, McGraw-Hill, 1948, c. 2.
2. Gunther, M.: Brit. J. Nutrition *6* (No. 2): 215, 1952.

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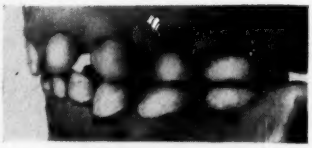

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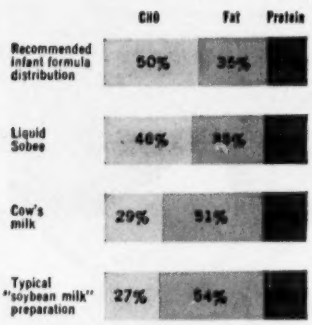

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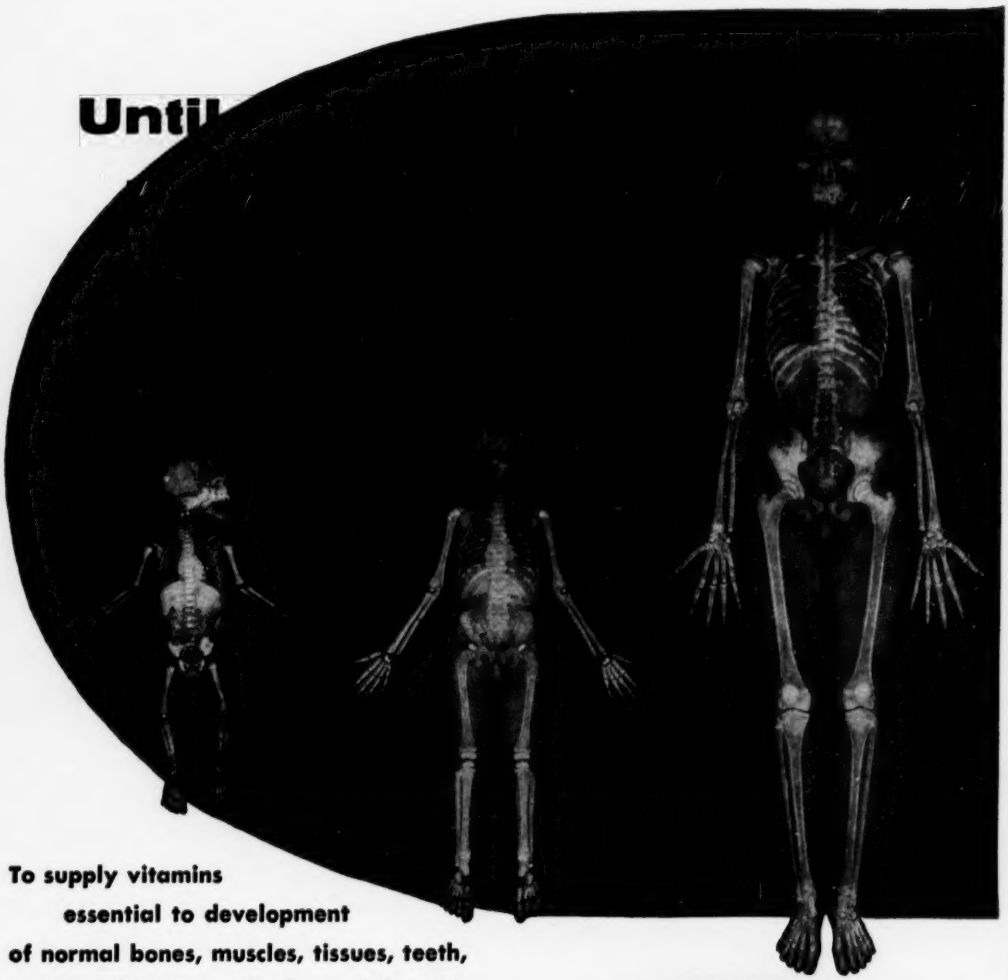

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